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ABSTRACT

This report updates the National Strategic Research Plan of the National Institute on Deafness and Other Communication Disorders (NIDCD) and reports progress made from 1991 through 1993 as required by the National Deafness and Other Communication Disorders Act of 1988 (Public Law 100-553) which established the Institute. An executive summary highlights major research accomplishments and opportunities in six program areas. Each of the following sections includes an overview of the program area; a listing of recent accomplishments in the field; the Institute's goals for the program area; a discussion of research opportunities, strategies, and priorities; and a summary of research recommendations. Individual sections address the following program areas in substantial detail: (1) hearing and impairment; (2) balance and the vestibular system; (3) smell, taste, touch, and chemosensory disorders; (4) voice and voice disorders; (5) speech and speech disorders; and (6) language and language impairments. Appendices include the text of Public Law 100-553 and a list of participants on panels addressing the different areas. (DB)

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National Institute on Deafness and
Other Communication Disorders

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National Strategic Research Plan

1991, 1992, 1993

U.S. DEPARTMENT OF
HEALTH AND HUMAN SERVICES
Public Health Service
National Institutes of Health
NIH Publication No. 95-3711

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FOREWORD

The National Deafness and Other Communication Disorders Act of 1988 became Public Law 100-553 (Appendix A) on October 28, 1988, establishing the National Institute on Deafness and Other Communication Disorders (NIDCD) within the National Institutes of Health (NIH). The law required that the Director, NIDCD, establish a National Deafness and Other Communication Disorders Program and prepare a plan to initiate, expand, intensify and coordinate Institute activities concerning disorders of hearing, balance, smell, taste, voice, speech and language.

In response to this mandate, a Task Force of scientific experts representing the seven program areas of the Institute convened in January 1989 to prepare the first National Strategic Research Plan which has guided the Institute over its first few years. The National Strategic Research Plan is also intended to inform the nation's scientists of areas of opportunity for research and to provide them with guidance as they formulate their own research plans. The Plan informs persons with communication disorders and their support organizations of past research accomplishments and potential future activities. In addition, the Plan is intended to inform members of Congress of research progress and future research opportunities in scientific areas within the purview of the NIDCD.

Public Law 100-553 requires the National Deafness and Other Communication Disorders Advisory Board to review, evaluate and update the plan periodically to assure its continuing relevance. To meet this legislative mandate, the National Advisory Board decided that it would update two of the six sections of the plan every year thus updating the entire plan within a three-year period. The National Advisory Board established six subcommittees, one for each section of the Plan which met and made recommendations for expert panel members, compared the research portfolio of the Institute to the National Strategic Research Plan, identified changes in the field since the Plan was developed, recommended levels and areas of research activity and suggested potential initiatives.

The Expert Panels on Balance and the Vestibular System and Language and Language Impairments convened on January 28 and 29, 1991; the Expert Panel on Hearing and Hearing Impairment on January 21 and 22, 1992; the Expert Panel on Voice and Voice Disorders on January 27 and 28, 1992; the Expert Panel on Speech and Speech Disorders on January 4 and 5, 1993; and the Expert Panel on Smell, Taste and Touch and Chemosensory Disorders on January 25 and 26, 1993. (Members of the expert panels are listed in Appendix B.) The results of their efforts are contained in this report.

FOREWORD

Members of the expert panels are due special thanks for giving of their talents and time in developing this document. Their meetings brought together representatives of a broad array of scientific disciplines within the areas of hearing, balance, smell, taste, voice, speech and language. Members of the expert panels shared their diverse ideas and worked diligently to achieve consensus on a comprehensive view of each field and a vision for the future. Subsequently, expert panel members refined their efforts with numerous revised texts.

Dr. Horst R. Konrad and Dr. Barry W. Peterson, Cochairpersons of the Balance and the Vestibular System Expert Panel; Dr. Rita S. Berndt and Dr. Laurence B. Leonard, Cochairpersons of the Language and Language Impairments Expert Panel; Dr. Jeffrey P. Harris and Dr. Mary Joe Osberger, Cochairpersons of the Hearing and Hearing Impairment Expert Panel; Dr. Thomas J. Hixon and Dr. Gayle E. Woodson, Cochairpersons of the Voice and Voice Disorders Expert Panel; Dr. Catherine T. Best and Dr. Raymond D. Kent, Cochairpersons of the Speech and Speech Disorders Expert Panel; and Dr. Claire L. Murphy and Dr. Michael T. Shipley, Cochairpersons of the Smell, Taste and Touch and Chemosensory Disorders Expert Panel deserve special appreciation. The update to the National Strategic Research Plan is a product of their experience, expertise and guidance. Along with their fellow expert panel members, they have formulated a plan for future research in the important scientific areas of the NIDCD.

James B. Snow, Jr., M.D.
Director
National Institute on Deafness and
Other Communication Disorders

PREFACE

The National Strategic Research Plan of the National Institute on Deafness and Other Communication Disorders (NIDCD) was prepared in April 1989 and presented the research recommendations of more than 100 eminent scientists in the seven program areas of the NIDCD. These areas are hearing, balance, smell, taste, voice, speech and language. This report contains an update of the 1989 plan.

More than 28 million Americans are believed to have impaired hearing, and this number is expected to increase substantially in the next few decades. Hearing impairments may result from genetic factors, infectious and inflammatory diseases, exposure to noise, aging, or other causes. Whatever the basis, these impairments have serious and far-reaching implications for the quality of life of those affected and represent enormous economic costs for treatment. Pursuit of research on normal and disordered hearing will lead to a better understanding of normal hearing processes and to improvements in the prevention and diagnosis of and treatment and rehabilitation for hearing impairment.

The vestibular system maintains balance and posture, regulates locomotion and other volitional movements and provides a conscious awareness of orientation in space and a visual fixation in motion. Disease, exposure to unusual motion or altered gravitational environments and aging can impair balance. A major consequence of vestibular disturbance is diminished capability and desire for purposeful activity. A better understanding of the normal function, development and aging of the vestibular system and the disorders which affect it would improve national health and reduce future health care costs.

The chemical senses (olfaction or the sense of smell and gustation or the sense of taste) detect and identify chemical stimuli in the environment. These stimuli include flavors, pleasurable aromas, scents and fragrances, as well as smoke and leaking gas, environmental chemicals and pollutants, hazardous vapors and gases. Thus, deficits in these senses can affect the ability of people to live full and productive lives. Research investigating chemosensory function and dysfunction throughout the human lifespan will lead to a better understanding of the basic processes of normal smell and taste, clearly characterize disordered function and elucidate mechanisms which underlie functional impairment, and thus provide the needed basis for prevention, diagnosis, treatment and rehabilitation of chemosensory disorders. Touch is an important communicative sense and is often utilized with the other senses. It provides information about objects in contact with the skin and, through transmitted mechanical disturbances, about events and objects at a distance. Research on the sense of touch takes on special importance because it is a communication channel for persons who are blind, profoundly deaf or deaf and blind.

PREFACE

Voice production or phonation is the generation and modulation of sound and is a subset of the more global process of speech production. In the context of communication, voice is an acoustical representation of language. Loss of the voice has profound psychological, social and economic consequences for the individual. Common disorders of the voice involve difficulties with pitch, loudness and quality and can be distinguished from articulation and fluency disorders, which present difficulties of speech sound production. Although the economic impact of voice disorders cannot be accurately assessed, these disorders can have devastating effects on those who suffer from them, interfering with their ability to function in a work or social setting. Research on prevention and diagnosis of and treatment and rehabilitation for voice disorders merits special attention in part because of how prevalent they are in our society.

Spoken language is the most distinct human faculty. Although humans can communicate in a variety of ways, including manual gestures and written alphabets, speech is the most common means of language expression in humans. One of the most important milestones in child development is the emergence of spoken language. Research on speech and its disorders offers a better understanding of how speech develops, how it is maintained through the lifespan, and how it is impaired by disease, trauma and other factors. Treatment and rehabilitation of individuals with speech disorders deserve the best efforts of an enlightened society.

Language is the uniquely human means of communication through which knowledge, belief and behavior can be explained and shared. The ability to manipulate language to satisfy needs and desires and to express thoughts, observations and values is an important human pursuit that directly influences the quality of life for any individual. Language impairments impede social development, academic performance, employment opportunities and economic self-sufficiency. Further research on the prevention, diagnosis and treatment of language impairments will help eliminate the social isolation and personal suffering imposed by these disorders on the affected individuals , their families and on society as a whole.

PREFACE

The update of the National Strategic Research Plan has provided an opportunity to evaluate the progress that has been made during the past three years and to assess future research needs and opportunities. The recommendations presented here are expected to lead to exciting advances in scientific knowledge and improve the quality of life for many people.

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National Institute on Deafness and Other Communication Disorders

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EXECUTIVE SUMMARY

Hearing and Hearing Impairment

More than 28 million Americans have impaired hearing, and this number is expected to increase substantially in the next few decades due to increasing longevity and the consequent overall aging of the population. Levels of hearing impairment vary from a mild but important loss of sensitivity to a total loss of hearing. The largest group of Americans suffering from hearing loss is the elderly. Age-related hearing loss affects 30 to 35 percent of the United States population between the ages 65 to 75 years and 40 percent of the population over the age of 75 years. Approximately one of every 1000 infants is born with a hearing impairment that is severe enough to prevent the spontaneous development of spoken language, and over 50 percent of these impairments are believed to be of genetic origin. The most common cause of hearing loss in children is otitis media. Otitis media is predominately a disease of infants and young children. This disease is estimated to account for over 10 million visits to the offices of physicians per year and to have a total annual cost of over $3.5 billion. A substantial number of hearing impairments are caused by environmental factors such as noise, drugs and toxins, and many acquired sensorineural hearing losses may result from a genetic predisposition to the development of hearing loss due to these factors. At least 15 percent of the population are affected by tinnitus, many so severely that it disrupts their lives.

Important progress has been made during the last decade in understanding the auditory system. Many insights into the function of the inner ear have been derived from in vivo and in vitro studies. Using in vitro biophysical approaches, characterization of the membrane properties of sensory and neuronal elements within the organ of Corti, the hearing organ, is beginning to provide us with an understanding of the molecular basis of auditory function. Sound energy is detected by inner hair cells, which are now understood as mechanoreceptors. It has been established that the transduction of stimuli by these cells is mediated by ion channels that are directly gated by mechanical forces. Progress has been made in understanding the motility of outer hair cells and how these mechanisms function in vivo. Changes in hearing have been shown to be the most closely associated with the loss of outer hair cells. The origin of the unique fluid movement within the cochlea and details of intracochlear blood flow have been established. In certain species, including the human, the hearing organ generates sound by spontaneous or evoked otoacoustic emissions. In humans, this phenomenon may be mediated by outer hair cells and has great promise for practical diagnostic use.

Major strides have been made in studying the regeneration of sensory cells in the ear. Sensory cells can be regenerated in the inner ear of cold-blooded animals, and in avian species in which the production of sensory cells normally ceases in early embryonic development, regeneration can also occur in young and adult birds. Regenerated hair cells originate from cells produced by the proliferation of supporting cells that survive at sites of damage in the inner ear. Since regeneration of sensory cells has not been demonstrated in mammals, sensory hearing impairment has been considered to be permanent and irreversible. Efforts are under way to stimulate regeneration of sensory cells in mammals. If these efforts are successful, they may provide a basis for the hope of stimulating regeneration of auditory hair cells in humans.

New information has been obtained concerning the encoding of complex signals transmitted from the auditory nerve to the brain. The relationship between the neural code for sound intensity, frequency and temporal characteristics and the perception of these stimulus variables has been further clarified. Molecular techniques have been used to identify many of the neurotransmitters and receptors involved at specific synapses throughout the auditory neural axis. Evidence suggests that efferent feedback pathways to the inner and middle ear may aid in the detection of signals in noisy environments and serve to protect the ear from acoustic injury. Neural plasticity or changes in the central nervous system have been described in response to enriched and deprived acoustic environments. New insights have been gained about the ways in which the brain creates maps of auditory space that interact with visual space.

Recent research in auditory psychophysics has produced a set of working models of auditory perception that have led to advances in the understanding of how human and nonhuman listeners assign identities and sources to the sounds that they perceive and how they recognize the communicatively important sounds of single and multiple speakers. There have been a number of important advances in the linking of psychoacoustic and physiologic research. Behavioral measures of frequency selectivity have been developed that allow comparison with electrophysiologic measures of auditory tuning which can now be used to characterize normal and impaired hearing. Increased understanding of the ability of the ear to distinguish changes in spectral shape from intensity changes has been achieved. Studies on the role of across frequency-band enhancement and interference effects on the detection and location of sounds are providing improved understanding of complex "real-world" auditory perception. Many new approaches are being used to characterize the location of sounds by humans which may lead to new possibilities for presenting sounds through prosthetic devices. Increased study of the role of perceptual learning, selective attention, auditory memory and organization in the formation of auditory percepts has contributed to the understanding of how we attend to multiple sources in complex acoustic environments.

Major advances have been made in identifying the genes that cause hearing loss. Recent accomplishments include the mapping of an Usher syndrome type 2 gene to the long arm of chromosome 1 and a gene for Waardenburg syndrome to the long arm of chromosome 2. Also, a gene for a dominant nonsyndromic form of hearing impairment has been mapped to the long arm of chromosome 5. At least 28 X-linked disorders involve hearing loss. Recent accomplishments include precise location of the gene causing albinism-deafness and tentative evidence of more than one X-linked gene for clinically identical forms of progressive mixed deafness. A further advancement in the field of genetics is the ongoing use of powerful tools of molecular biology to clone the genes for inner-ear development and the assembly of human and animal cochlea-specific cDNA libraries.

The role of genetic factors in acquired sensorineural hearing loss has recently been underscored by the demonstration of a genetically controlled mitochondrial disorder which predisposes the host to aminoglycoside ototoxicity. Such models will enable researchers to understand how and which ototoxic metabolites cause damage to the cochlea. Similar factors may prove to be important in the development of presbycusis, and the identification of mouse models of this condition will also help elucidate potential new therapies for sensorineural hearing impairment.

Recent progress utilizing modern immunobiologic techniques has demonstrated that the inner ear is immunoresponsive and comes under the influence of the host's immune system. Furthermore, it has been shown that immune reactions within the inner ear occur as a result of both the host's normal defense mechanisms as well as an immune response gone awry in the form of autoimmunity. Recent evidence, in fact, has shown that some patients with rapidly progressive deafness have autoantibodies directed against their inner ear and if recognized and treated early, their hearing can be restored. Applications of immunologic assays may become available to make this diagnosis and to open new avenues for treatment. The application of these techniques also may prove to be helpful in the diagnosis of perilymph fistulae.

Recent development of animal models of bacterial and viral infections of the labyrinth and meninges has led to a greater understanding of the development of sensorineural hearing impairment associated with these conditions. The time course, the role of immunity and inflammation, the routes of spread and therapeutic interventions are beginning to be understood for the first time. Newer forms of anti-inflammatory agents, antibiotics and antiviral drugs may find rapid application in the treatment for these conditions with the advent of suitable animal models in which to test their efficacy. Additionally, these models will allow a greater understanding of why and to what degree infants and children are susceptible to ototoxic drugs used in the treatment of infections.

Due to the prevalence, long-term sequelae and cost to our society, otitis media continues to be an important focus of research. Important progress in the understanding of the epidemiology and pathophysiology of otitis media has been made. Studies of the eustachian tube have provided new information on tubal compliance, surfactant-like substances, neural connections, mucociliary clearance and the effects of adenoidectomy and drugs on its function. Recent studies also have revealed the importance of cellular regulation, differentiation and receptor expression in the pathogenesis of otitis media. Application of immunocytochemistry has led to advances in our understanding of the filament proteins, neuropeptides, oxidative enzymes, immunocompetent cells and inflammatory mediators involved in otitis media. New evidence has surfaced which shows the importance of prior viral infection in the development of otitis media. Research at the cellular and molecular levels has begun to characterize the bacterial-cell genome to understand better adherence of bacteria to epithelial cells and antibiotic resistance, as well as cell-membrane receptors involved in bacterial invasion and how properties of the bacterial-cell wall and its breakdown products lead to middle-ear inflammation. The role of local and systemic immunity has also received recent attention by the demonstration that the middle-ear immune response may be manipulated by donor T-lymphocytes which are primed by oral antigen. Such studies might lead to newer methods of prevention by rendering the host immunologically tolerant to the antigens liberated during otitis media so that inflammation is abrogated. Current research also suggests that impaired immunity or its delayed maturation may predispose certain children to otitis media.

Important research on developing new and more immunogenic vaccines for the prevention of otitis media caused by nontypable *Haemophilus influenzae* and *Streptococcus pneumoniae* (pneumococcus) are now under way. They have been encouraged by the success of vaccines with *Haemophilus influenzae* type b polysaccharide-protein conjugates in the prevention of meningitis in infants and young children, a major cause of profound hearing impairment. Clinical studies have also made strides in the diagnosis and antibiotic and surgical treatment for otitis media.

Recent advances in exploring the cause of otosclerosis, a disorder which affects one out of every 100 adults in this country, are promising. With the use of immunohistochemical techniques, viral antigens of rubella and rubeola have been found in the active lesions of this disease and newer ultrastructural studies are beginning to shed light on the mechanism of bone remodeling seen in this condition.

Studies of the host factors which lead to the development of cholesteatoma are emerging as well as the role of inflammation, enzymes and factors involved in bone resorption and remodeling. Despite extensive clinical efforts, chronic suppurative otitis media and cholesteatoma still account for the majority of conductive hearing loss cases in adults in the United States. The development of biocompatible, middle-ear implants for the correction of conductive hearing loss has resulted in great progress. Newer, prosthetic, ossicular and canal-wall implants are being developed and employed in clinical trials to establish their efficacy. Additionally, there has been important development of partially or fully implantable hearing aids for the correction of conductive hearing losses for which routine hearing aid applications have failed.

Considerable progress had been made in hearing aids and other auditory prostheses. Digital and programmable hearing aids with improved signal processing are being developed and fitted clinically. In addition, a variety of noise reduction schemes are being incorporated into hearing aids. The multichannel cochlear implant has become a widely accepted auditory prosthesis for children and adults who receive no benefit from conventional hearing aids. The vast majority of adult cochlear implant recipients derive substantial benefit in conjunction with speechreading, and many can communicate effectively without speechreading. Children, including the prelingually deafened, also demonstrate substantial benefit from implants, particularly with continued use. New sound processing techniques based on high-rate, nonsimultaneous (interleaved), pulsatile stimulation have been shown to improve the effectiveness of cochlear implants. An important development is the application of neural prostheses to the auditory brain stem in individuals with destruction of the nerves of hearing due to bilateral acoustic neurinomas or head trauma. Studies of methods of tactual communication used by deaf and blind persons demonstrate the capacity of the skin and the proprioceptive system as a communication vehicle and provide a basis for the development of tactile aids as alternatives for powerful hearing aids and auditory prostheses.

Recent accomplishments in the area of auditory rehabilitation include the use of computer-controlled video and audio laser disc systems for fully or semi-automated instruction and the increased understanding of the contributions of context and prior knowledge to the perception of spoken language from impoverished sensory input.

The areas of assessment and diagnosis have benefited from the development of noninvasive methods for measurement of the acoustic properties of the external and middle ears (acoustic immittance), computer-based techniques for assessment of sound-evoked electrical activity in the cochlea (electrocochleography) and in the brain (auditory brain stem and cortical responses) and the discovery of spontaneous and evoked emission of sound from the inner ear (otoacoustic emissions). Otoacoustic emissions hold great promise for the precise evaluation of defects in the inner ear and for the early identification of hearing impairment in infants.

Research Opportunities in Hearing

Transduction and Homeostasis

- Measure the mechanical changes in hair bundles during transduction and adaptation and determine how these mechanical changes affect basilar-membrane motion.
- Elucidate the mechanism of outer-hair-cell motility and investigate the role of this process in frequency tuning on the basilar membrane.
- Relate the unique structure of the hair cell's afferent synapse to its role in sensitive, high-frequency synaptic transmission and identify the hair cell's neurotransmitter and its postsynaptic receptor and signaling mechanisms.
- Identify and characterize the molecular substrate underlying transduction, motility and cellular homeostasis.
- Examine the homeostatic processes that regulate the cochlear environment, including the control of blood flow, ionic balance and intercellular communication.
- Construct cDNA libraries representing messages for proteins involved in transduction, motility and ionic regulation; probe the libraries in an effort to identify and sequence the proteins that are the transduction channel, the adaptation motor, the afferent transmitter receptor and growth-factor receptors.

Sound Processing in the Brain

- Study the functional connections of neurons and synaptic mechanisms at all levels of the auditory system.
- Relate neurophysiologic descriptions of the auditory system to animal and human psychophysical data.
- Characterize fully the afferent and efferent auditory systems.
- Study the potential for central reorganization subsequent to peripheral or central injury,

determining the plasticity of the mature auditory system and the impact of modified auditory input upon its organization.

- Develop models to provide concise descriptions of normal and abnormal auditory function.

Auditory Perception

- Define the relations between complex acoustical signals and the resulting perceptual experiences of listeners.
- Elucidate the perceptual correlates of sound coding in the auditory nervous system.
- Enhance the understanding of sound location in animals and humans.
- Relate emerging knowledge about perceptual organization to the development of a comprehensive model for auditory perception of spoken language.
- Extend research conducted on listeners with normal hearing to study the consequences of sensorineural hearing loss on the perception of complex sounds and spoken language.

Development, Aging and Regeneration

- Assess the normal life cycle of the auditory system, including the definition of critical periods for the development of auditory processes.
- Evaluate the limits of neural plasticity in the auditory system.
- Define the influences of environmental, nutritional and pathologic factors that compromise the normal life cycle of the auditory system.
- Study the embryonic mechanisms for the formation of the normal ear and characterize the mechanisms underlying normal cell proliferation and differentiation.
- Study the developmental course of complex sound and speech perception in infants and young children.
- Elucidate the many aspects of age-related hearing loss in animals and humans.
- Isolate and identify molecular events that evoke proliferation leading to the replacement of lost sensory cells.
- Assess the roles of known and suspected growth factors that may influence the production and development of replacement sensory cells and the formation and maintenance of their contacts with neurons.
- Explore the molecular, morphologic, physiologic and

behavioral consequences of sensory cell regeneration.

- **Identify the mechanisms that determine neuronal survival and explore paradigms that may protect and maintain auditory neurons after trauma or deprivation.**

- **Characterize the morphogenetic processes of the embryonic ear.**

- **Identify the intercellular signals that regulate developmental specialization of cells that perform the sensory and supporting functions of the cochlea.**

- **Determine which growth factors mediate the trophic interdependence between sensory cells and neurons in the auditory system and assess the strength and the timing of those interactions in normal development and during regeneration.**

- **Investigate the potential for sensory cell replacement and regeneration in mammals.**

- **Study the role of electrical stimulation in prolonging neuronal survival.**

Research Opportunities in Hearing Impairment

Hereditary Hearing Impairment

- **Map, isolate, clone, sequence and characterize genes responsible for hearing impairment in humans and animals.**

- **Solicit the participation of families in studies of hereditary hearing impairment. Educate professionals serving people with hearing impairment regarding selection criteria for these families.**

- **Develop clinical and physiological tests which identify carriers of recessive hearing loss genes.**

- **Develop comprehensive inner ear-specific cDNA libraries from humans and laboratory animals.**

Acquired Sensorineural Hearing Loss

- **Study the incidence, pathophysiology and treatment of hearing loss and ear disease associated with human immunodeficiency virus and the opportunistic infections it causes.**

- **Study the incidence, pathophysiology, diagnosis and treatment of hearing loss associated with viral and bacterial infections.**

- **Study the natural history, biology, treatment and rehabilitation following treatment of neoplasms which affect the temporal bone.**

- **Study the effects of trauma, environmental factors and ototoxic drugs on hearing; new means of establishing the causal relationship** of the hearing impairment to the traumatic event or injurious agent; improved screening techniques for prevention; location of the insult within the auditory system; and identification of the molecular mechanisms underlying this damage so that strategies for treatment can be developed.

- Study the possible causes of acquired sensorineural hearing loss of infancy to establish precise causes so that preventative interventions can be developed.
- Study the normal immune host responses involved in diseases of the middle and inner ear.
- Establish and investigate animal models of autoimmune sensorineural hearing loss, determine the inner-ear targets of autoimmunity, develop specific and sensitive diagnostic tests for this condition in humans and conduct controlled treatment trials to determine effective and safe therapeutic intervention.
- Study the idiopathic forms of hearing loss, such as otosclerosis and perilymphatic fistula, with attention toward establishing a cause, improving diagnosis and determining efficacy of treatment.
- Determine the natural history, pathogenesis and treatment of tinnitus.
- Perform clinical trials to determine the most efficacious treatment for the various causes of sensorineural hearing loss.
- Study the natural history, epidemiology, diagnosis, pathogenesis and treatment of Meniere's disease.
- Establish more sensitive diagnostic tests for viral deafness, separation of peripheral from central causes of hearing loss, neurofibromatosis type 2 and those at increased risk for noise-induced hearing loss and ototoxicity.
- Apply newer research techniques involving molecular biology, immunohistochemistry, electron microscopy and computer-assisted reconstruction to the study of the temporal bone.
- Establish a national consortium to create cDNA libraries of the inner ear so that this technology can be made available to investigators in the field.
- Develop national registries to collect epidemiologic data on hearing loss and other diseases which affect the ear.

Otitis Media, Otosclerosis and Other Middle-Ear Disorders

- Study the epidemiology and incidence of otitis media among multicultural populations with attention to environmental versus genetic factors.

- Study the anatomy, biochemistry and development of the eustachian tube and its role in otitis media and maintenance of middle-ear gas composition.
- Study the cellular elements and their function in the middle ear.
- Study the microbiology, immunology and biochemistry of the middle-ear inflammatory response.
- Study the role of local and systemic immune responses in the pathogenesis and recovery from otitis media.
- Develop vaccines for the prevention of otitis media and meningitis.
- Develop diagnostic measures for otitis media in infants under six months of age.
- Study existing and new treatment modalities in otitis media to establish their efficacy and safety.
- Study the long-term sequelae of otitis media on middle- and inner-ear function, middle-ear and mastoid pathology and speech, language, perceptual and cognitive development.
- Study the epidemiology and the molecular and cellular mechanisms involved in the pathogenesis of otosclerosis.
- Develop a precise diagnostic test or assay for perilymphatic fistula.
- Study the micromechanics of the conductive hearing apparatus and develop improved middle-ear implants and electromechanical or electromagnetic drivers of the ossicular chain.

Assessment, Diagnosis, Treatment and Rehabilitation

- Develop and validate new procedures to identify hearing loss and evaluate the perceptual consequences of hearing loss.
- Develop and evaluate new techniques for effective auditory rehabilitation of children and adults with hearing impairment.
- Continue the development and evaluation of sensory aids for persons with hearing impairment including hearing aids, cochlear implants, auditory brain stem implants, tactile aids and speechreading supplements.
- Continue the development and evaluation of visual technologies for individuals with hearing impairment.

Balance and the Vestibular System

Approximately two million adults in the United States have chronic impairment from dizziness or a balance problem. The cost of medical care for patients with balance disorders exceeds one billion dollars per year. Balance disorders increase in frequency in the older age groups and by age 75 years become the most common reason for seeking help from physicians. Over 50 percent of elderly patients interviewed at home complain of balance disorders. When one adds the cost of injury caused by imbalance and the lives and aircraft lost by the armed services due to balance-related disorientation, the cost becomes truly staggering. Since our population is aging, more Americans will suffer from balance disorders in the future. A better understanding of the normal function, development and aging of this system and the disorders which affect it would certainly improve national health and reduce future health care costs. The need to understand motion sickness and orientation in high technology aircraft and altered gravity environments is also pressing. Our nation increasingly relies on such aircraft for national defense and has reaffirmed major space exploration as a national goal.

The primary receptors of the vestibular system are located in the inner ear and the system is required for the sense of orientation in space, for maintaining balance and posture, for regulating locomotion and fine motor control and for the ability of a person to fix in view and follow an object when the object or the person is in motion. The brain also integrates information from the vestibular detectors and their central connections with information from the eyes, skin, muscles and joints to create perception of body orientation and of motion of the body with respect to space. Because the system has many components, there are many symptoms that reflect its malfunction.

A current view of the vestibular system is that the vestibular receptor organs "process" the forces associated with head acceleration and changes in head position relative to gravity. Nerves going to brain control centers are excited, and the brain uses these signals to develop a sense of orientation and to activate automatically the muscles that subserve movement of the eyes, locomotion and posture. Many of the vestibular pathways in the central nervous system are organized into reflex pathways that serve to stabilize and coordinate movements of the eyes, head and body. These processes are collectively referred to as the vestibular reflex systems. One such reflex, the vestibulo-ocular reflex, causes the eyes to move in reaction to head motion.

Orientation is a complex function that allows a person to know the relationship of parts of the body to the environment in a dynamic and reciprocal interaction. Maintaining orientation and balance requires the integration of information from many sources, especially the ears, eyes, skin, muscles and joints, and transforming these signals into coordinated patterns of muscle activity. Because vestibular signals interact with all the major sensory systems and involve major brain centers, a large number of disease processes can impair balance.

Motion sickness can occur with exposure to conflicting orientation cues, perceptions of space and motion signals. A high incidence of motion sickness occurs in pilots being trained in stationary flight simulators. Trainees learn behavioral responses to prevent the development of motion sickness. Space motion sickness, which affects a large number of astronauts, is a major unsolved problem for space travel.

During the past decade, new protocols and computer-based techniques have been developed that can help in the evaluation of gaze and balance disorders. Vestibular reflexes, posture and the interactions of different sensory inputs to the central nervous system can be measured precisely. Among the most remarkable properties of the vestibular and balance control systems are their ability to maintain useful functioning responses to many novel motion environments and their ability to adapt to abnormal function in one or more of their components. Recent accomplishments include a recognition of the essential role of adaptive plasticity in the normal function of the vestibular system, development of improved mathematical models of vestibular reflexes and an anatomical description of the basic circuitry in the brain stem subserving the vestibular-ocular reflexes. Important advances have also been made in understanding the structure and function of the vestibular receptor organs and the way in which their activity is modulated by efferent signals originating in the brain. Work is now beginning to determine the neurotransmitters utilized by neural circuits in the vestibular system, to define the changes that occur in this system during development and aging and to devise efficient techniques for rehabilitating patients with vestibular dysfunction.

Advances in diagnosis include computer-based technology to identify, quantify and locate the source of balance dysfunction. The National Research Council recently suggested methods for standardization of testing, test interpretation and technician training. Ongoing improvement in magnetic resonance imaging provides for detection of smaller, more operable neoplasms and the detection of several degenerative brain disorders including cerebral atherosclerosis, multiple sclerosis and spinocerebellar disorders. These developments have been complemented by the ability of dynamic computed tomography to measure blood flow in various parts of the brain. Such techniques result in early diagnosis and improve the outcome of surgery. They also allow us to evaluate better the progression of disease, design clinical research programs and evaluate the effects of treatment. Some autoimmune disorders and ataxic syndromes can now be diagnosed and treated with medication based on a better understanding of immune mechanisms and the role of brain transmitters. There are recent improvements in our understanding of the association between balance symptoms and the social, psychological and psychiatric disorders which frequently accompany them. This understanding allows us to manage these patients in a comprehensive fashion rather than to focus on isolated balance disorders.

Major Basic Scientific Opportunities

There are five broad, high-priority areas for basic vestibular research: signal transduction by vestibular end-organs; reflex control of posture and gaze; sensory integration in spatial orientation, perception and motion sickness; adaptive changes in vestibular function; and development and aging of the vestibular system. Within each area, opportunities exist for research at the levels of: behavior, kinesiology and biophysics; anatomy and physiology; cellular properties, biophysics and metabolism; pharmacology, molecular biology and genetics; and mathematical and computer modeling. These opportunities can be summarized as follows:

Signal Transduction by Vestibular End-Organs

Important goals are to understand how vestibular end-organs convert head movements into neural signals and to determine the way in which this conversion is modulated by efferent projections from the brain to the end-organs. Research is needed to:

- Describe the motions of the cupulae and otolithic membranes in response to head movements and examine the possible role of hair cell motility in modifying these motions.
- Determine the distribution and organization of otolithic organ and semicircular canal inputs to the vestibular nuclei and cerebellum and elucidate the function of the vestibular efferent system in behaving animals through anatomic and physiologic research.
- Characterize the biophysical properties of hair cells and afferent fiber terminals. This research should include studies of the hair cell transduction channel, the basolateral currents within hair cells and the efferent actions on both hair cells and afferent nerve terminals.
- Conduct molecular biological studies which isolate and characterize the molecular components of the transduction channel and associated regulatory proteins.
- Identify neurotransmitters which mediate peripheral vestibular function.

- Investigate metabolic requirements of the sensory organs and neurons in the inner ear and the mechanisms of production of inner-ear fluids and transduction elements (cristae and maculae).

- Develop dynamic models that predict and explain patterns of afferent fiber activation on the basis of anatomical and biophysical properties of end-organs.

Reflex Control of Posture and Gaze

The goal is to understand the structure and function of neural circuits that transform vestibular sensory input into the motor output required for control of posture, locomotion, fine motor activities and gaze. Research is needed to:

- Characterize the behavioral strategies and neural mechanisms used to determine posture and gaze during active and passive motion and during combinations of linear and angular acceleration in three-dimensions. Studies are also needed to define the effect of exposure to altered gravito-inertial fields on vestibular reflexes and their potential clinical consequences.

- Characterize the anatomic and physiologic properties of neuronal pathways that constitute the vestibular system in animal models and normal humans. It is especially important to identify pathways involved in vestibular reflex control of neck, axial and limb muscles and to determine the signals they carry. Emphasis should also be given to understanding the neural substrates of otolithic organ reflexes and postural stabilization.

- Correlate structure and cytochemistry of neurons in different vestibular circuits with their response characteristics.

- Characterize the biophysical, molecular and pharmacological properties of specific groups of relay neurons in postural and gaze reflex pathways.

- Develop multidimensional models that explore the neural basis of dynamic and spatial transformations in vestibular reflexes.

Sensory Integration in Spatial Orientation, Perception and Motion Sickness

Understanding of the vestibular system requires knowledge of how vestibular signals interact with information from other senses to generate perceptions, movements and motion sickness. Research is needed to:

- Describe sensorimotor and perceptual reactions to complex combinations of linear and angular accelerations and determine how vestibular, visual and proprioceptive inputs interact to generate perceptions of space and body motion.

- Conduct anatomic and physiologic research to characterize the neural mechanisms that combine otolithic organ, semicircular canal, visual and somatosensory information to generate perceptual and postural responses and that generate motion sickness.

- Characterize the neural and humoral mechanisms associated with motion sickness and vertigo at the cellular and molecular levels.

- Develop models that incorporate and test the understanding of the neural basis of postural and gaze control during active and passive motion.

Adaptive Changes in Vestibular Function

Studies of vestibular adaptation can both reveal basic principles of motor learning and lead to strategies for enhancing recovery from vestibular lesions. Research is needed to:

- Determine at the behavioral level, both the extent to which the adaptive system can compensate for vestibular dysfunction and the sensory cues that are important in producing this compensation. Adaptive changes in both rapid and slow components of the VOR and in postural reflexes should be studied.

- Conduct anatomic and physiologic research to determine where in the brain stem and cerebellum the neural changes responsible for adaptive alteration of vestibular reflexes occur and how these changes lead to the observed alterations in behavior.

- Characterize the biophysical changes that occur at various neural sites during the adaptive process.

- Analyze the pharmacologic and molecular bases of adaptive changes and the way in which they depend on expression of molecular mechanisms such as proto-oncogenes, second messengers or humoral factors.

- Develop models that account for adaptive changes at both the biophysical and neural circuit levels.

Development and Aging of the Vestibular System

Knowledge in this area will both help us deal with developmental disorders and age-related declines in vestibular function and also contribute to basic understanding of vestibular mechanisms. Research is needed to:

- Characterize at the behavioral level the progression of perceptual and reflex function during development and aging.

- Conduct anatomic and physiologic research to determine the mechanism(s) underlying development of central vestibular pathways, their relation to development of peripheral end-organs and the ontogenetic sequences of connectivity between vestibular neurons and motor and higher sensory centers in the brain.

- Study how membrane and synaptic properties of hair cells and vestibular sensory and motor neurons change during development and aging and examine the roles of neural activity and neurotransmitters in producing those changes at the cellular level.

- Determine the neurotransmitters present in vestibular brain stem nuclei over the course of development, maturation and aging.

Major Clinic Scientific Opportunities

There are six broad high priority areas for clinical vestibular research: prevalence and environmental factors; anatomic, physiologic and molecular bases; diagnostic methods and testing procedures; adaptive mechanisms; and medical and surgical therapy. These opportunities can be summarized as follows:

Prevalence and Environmental Factors

It is important to develop a better understanding of disease prevalence and possible associated environmental factors. Research is needed to:

- Assess the distribution of balance disorders among different sectors of the population (including age, gender, genetic background and geography).

- Identify environmental and occupational hazards that adversely affect balance.

- Carry out a demographic study to evaluate the deleterious effects of prescription and over-the-counter medications which may produce central or peripheral vestibular alterations.

Anatomic, Physiologic and Molecular Bases

A better understanding of anatomic, physiologic and molecular bases of normal and abnormal balance processes is needed.

- Determine modifications of neuronal vestibular pathways in animal and human pathologic specimens with known vestibular dysfunction.

- Analyze the molecular and pharmacologic properties of specific groups of relay neurons in postural and gaze reflex pathways. The development of these properties from embryo to adult vestibular systems should be traced and changes that accompany aging examined.

- Determine the coexistence of multiple neurotransmitters within single vestibular synapses.
- Determine the excitatory and inhibitory neurotransmitters in the vestibular portion of the brain stem nuclei during development, maturation and aging.
- Develop animal models to study the pathophysiology of vestibular diseases.
- Examine structural changes in vestibular pathways in animal and human pathologic specimens with known vestibular dysfunction.
- Investigate the molecular basis of acquired and congenital inner-ear disorders in humans and animal models.
- Study and correlate peripheral and central pathologic abnormalities with biochemical and molecular changes in human subjects with well-studied disease.

Diagnostic Methods and Testing Procedures

Improved tests of balance function, a more standardized method of testing and research on pathology are needed.

- Develop new tests to evaluate otolithic organ and vertical semicircular canal function in humans, including freely-moving subjects.
- Develop tests to define the contributions of neck receptors to normal gaze and balance function and to vertigo and imbalance in pathologic conditions.
- Develop new tests for vestibular function involving non-invasive recording of neural activity and/or reflex responses elicited by specific mechanical or electrical stimuli that activate vestibular afferents.
- Develop new and improved methods for the evaluation of posture under static and dynamic conditions.
- Develop standards for the more commonly used diagnostic tests in the vestibular test battery.

- Develop improved psychophysical methods for evaluation of vestibular function in health and disease.
- Develop animal models to study the reliability and validity of new vestibular tests.
- Develop methods to detect immunologic and autoimmune inner-ear disorders and neoplasms for the diagnosis of vestibular system disorders.
- Validate currently accepted diagnoses or new diagnoses based on clinical pathologic correlation.
- Conduct serial (longitudinal) studies of the changes in vestibular tests in patients with well-defined pathologic processes.

Adaptive Mechanisms

Adaptive mechanisms play an important role in normal balance function, compensation for disease and rehabilitation.

- Analyze the molecular and pharmacologic bases of adaptive changes in the vestibular system.
- Investigate the use of pharmacologic agents to modulate changes in adaptive compensation.
- Extend studies of adaptive behavior to consider the conditions of unilateral and bilateral labyrinthectomy in an attempt to understand the response to vestibular damage.
- Determine if there is a critical period for the initiation of vestibular exercises to facilitate recovery following the sudden onset of vestibular loss or dysfunction in humans.
- Determine the optimal characteristics of vestibular stimulation necessary to facilitate recovery in different vestibular disorders.

Medical and Surgical Therapy

Medical and surgical therapy is frequently based on insufficient determination of efficacy. Standardized reporting of results is critical, and the efficacy of treatment should be determined.

- Perform multicenter, prospective, controlled clinical trials which:
  - evaluate medical therapy for vestibular symptoms.
  - evaluate osmotic or renal loop diuretics for the treatment of episodic vertigo.
  - compare medical to surgical ablative therapy in Meniere's disease.
- Study the pathologic effect of vessel loop compression on the vestibular nerve and the effectiveness of vessel loop relocation.

- Study the anatomic, physiologic and pharmacologic central nervous system correlates of neurectomy (partial and total) compared to labyrinthectomy in appropriate animal models.
- Determine the effect of surgical manipulation of the cochlear nerve and the facial nerve intracranially and in the internal auditory canal.
- Determine the effect of the peripheral and central molecular, biochemical and structural changes following various ablation procedures, e.g., labyrinthectomy and partial and total vestibular neurectomy.

Smell, Taste and Touch and Chemosensory Disorders

Basic Science Opportunities

Dramatic progress has been made in understanding the molecular bases of the senses of olfaction (smell), gustation (taste) and taction (touch) in the last five years. In the chemical senses of smell and taste, the stimuli are chemicals which make contact with molecular receptors on the surface of the receptor cells and induce a chemical reaction in the receptor cell that results in the initiation of a neural impulse to the brain. This process is known as transduction. Using biophysical approaches at the level of the cell, odor and taste transduction have been found to involve the activation of ion (electrically charged atom or group of atoms) channels in the cellular surface membrane that allow ions, such as sodium and calcium, to flow through the membrane as well as biochemicals that serve as a second level of messenger from the stimulus receptor complex to the mechanism for propagation of a neural impulse.

Molecular biologic techniques, such as the polymerase chain reaction (PCR) which allows the production of large quantities from tiny quantities of specific proteins, are being employed. The PCR has been used to clone (amplify) and identify a large new family of genes that encode the olfactory receptor molecules. The olfactory receptor molecules are large proteins that weave from the inner to the outer surface of the cell membrane seven times and are called seven-transmembrane domain proteins. Chemically repetitious segments of these proteins are spoken of as gene motifs and are responsible for the specificity of the molecular receptors to certain odorants. This mechanism lends itself well to the recognition of a vast array of odorants. Similar approaches are expected to bring equally dramatic advances in identification of taste receptors in the near future.

These and other cellular and molecular advances create unparalleled research opportunities for solving fundamental problems ranging from the peripheral encoding of chemosensory stimuli to the characterization of all of the gene motifs that confer molecular specificity to the chemosensory and touch systems.

The receptor cells of the senses of smell and taste are continually replaced throughout life and regenerate when injured. Exciting progress is being made toward understanding the cellular and molecular mechanisms responsible for the replacement of these receptor cells as well as the mechanisms that regulate development and the unique regenerative capabilities of the olfactory and gustatory systems. It has been found that glial cells which were formerly thought to provide principally structural support in neural tissue have been found to play important roles in the development and regeneration of receptor cells. Nerve growth and other trophic factors are now known to serve vital regulatory functions in this process. Also of interest are the newly found genes responsible for neural compartmentalization and pattern formation. It is now known that the axons (central extensions) of the olfactory receptor cells regulate neurogenesis (nerve cell development) and neural differentiation in the telencepholon (front part of the brain from which the cerebral hemispheres develop).

There is evidence that the axons of the first order (first in a chain of neural cells) taste neurons are essential for the nurture of the taste receptor cells and are capable of plasticity (change and reorganization) in the taste portion of the central nervous system.

Olfactory receptor cells are neurons, and they can now be grown in culture where they multiply and differentiate into nerve cells. In the field of neurobiology, exciting advances include the development of genetically transferred (altered) cells and the use of organotypic slice cultures. Organotypic slices of an organ like the brain can function, in a limited way, like an organ. Organotypic slice cultures are being used to isolate the molecular mechanisms that regulate synaptic targeting (junctional meeting) of two or more nerve cells and neural circuit development. These techniques offer powerful approaches for pinpointing the cellular and molecular mechanisms that specify and regulate development, regeneration and plasticity in the olfactory, gustatory and tactile systems.

New, unprecedented cellular and molecular advances in clarifying mechanisms of peripheral reception and transduction, and neural development have increased our understanding of central processing of chemosensory information. For several decades, the field has been dominated by issues of reception and transduction. Recognizing that these questions yield new approaches to molecular biology and membrane biophysics, there is a growing appreciation of the magnitude of the conceptual research problems that lie beyond the periphery in the central neural networks that analyze peripheral input. Transformation of this information allows perception and discrimination and regulates the variety of behaviors and endocrine responses triggered by odorants and tastants. For example, it is not even know that neurotransmitters are used by first order sensory neurons in the smell and taste systems. Dynamic approaches being used to analyze central neural network function in other sensory systems have received little attention in the smell, taste and touch systems. In touch, although there has been important progress through the use of combined psychophysical-neurophysiological techniques in trained primates, little use has been made of this powerful approach in the chemical senses. While the broad outlines of smell and taste circuits are known, the synaptic organization and the transmitters used by these networks are largely unknown. These challenging problems and the range of powerful techniques already in use in other areas of neuroscience create a variety of research opportunities in the senses of smell, taste and touch.

Stimulus Characterization and Detection, Signal Transmission and Perireceptor Events

Molecular Bases of Olfactory Reception

- Characterize the specific odorant recognition profiles of individual receptor molecules.
- Determine the coupling mechanisms between different receptors and second-messenger systems.
- Apply biophysical and optical recording techniques to determine stimulus specificity profiles and epithelial distributions of olfactory receptor neurons.
- Characterize the molecular mechanisms that determine olfactory-specific gene expression.
- Determine if genes that are selectively expressed in olfactory neurons have the same regulatory elements.
- Explore olfactory gene function by selective deletion of genes associated with reception, transduction, trophic interactions and neurotransmission.
- Identify the roles of newly discovered transcription proteins in determining olfactory-specific gene expression.
- Evaluate the metabolism of xenobiotic molecules and the distribution and role of odorant binding proteins.
- Identify the neurotransmitter(s) used at the first synapse of olfactory receptor neurons.
- Use new reverse transcriptase and polymerase chain reaction techniques to identify gene expression at the single-cell level.
- Use transgenic models for the study of receptor expression; sensory

cell replacement; events determining cell death and replacement and connection with central targets.

- Generate functional cell lines to study cellular mechanisms of transduction and plasticity.
- Investigate possible genetic bases of chemosensory deficits in human and animal models.
- Learn how receptor specificity is determined by assessing the roles of sensory stimulation in gene regulation, connection with target and location in the receptor neuroepithelium.
- Evaluate the roles of anterograde and retrograde transneuronal influences on the development and phenotype of olfactory sensory cells and their target neurons.
- Determine the physicochemical and molecular correlates of odorant and nasal irritant potency and develop models to predict efficacy.

Taste Perception and Transduction

- Locate, isolate and characterize macromolecules used in taste detection and transduction.
- Apply electrophysiological and optical recording techniques to the study of taste transduction.
- Use existing animal strains and produce new animal models with specific taste deficits to identify and clone macromolecules involved in taste cell processing.
- Characterize salivary composition and its possible alteration by taste stimuli and hormonal factors.
- Identify potential tastant-binding proteins critical to the delivery of taste stimuli to the receptor cells.
- Determine molecular correlates of taste and oral irritant potency; develop quantitative structure-activity models.

Taste Receptor Tuning

- Apply electrophysiological and optical recording techniques to characterize the response of single taste cells to a variety of taste stimuli.
- Combine morphological, physiological, biochemical and molecular techniques on single taste cells to determine whether specific taste cell types respond selectively to specific taste stimuli.

Cellular Interactions within Taste Buds

- Identify neurotransmitters and neuromodulators and their receptors in taste buds.

- Characterize the integrative properties of taste buds in signal processing.

- Investigate the trophic influences in taste bud development and maintenance using cell, tissue and tissue-slice culture techniques.

Hormonal and Systemic Influences on Taste Functions: Taste and Addiction

- Use specific chemical probes to test for the presence of hormone receptors in taste buds.

- Characterize nutritional, hormonal and systemic influences on sensory responses of taste buds.

- Formulate and test hypotheses regarding the mechanisms underlying systemic influences on taste function.

- Determine the role of early taste experience in the development of brain opiate systems and their role in addiction and pain management.

Psychophysical and Neurophysiological Studies of Smell, Taste and Touch

- Investigate psychophysical and neurophysiological correlates of spatial-temporal touch information.

- Develop and evaluate tactile displays.

- Encourage coordinate psychophysical and neurophysiological studies of smell and taste function.

Central Mechanisms: Neural Networks and Functional Integration

Olfactory Projections

- Carry out functional analyses of olfactory projection patterns by monitoring excitation and inhibition with such techniques as electrophysiological recording, voltage sensitive dyes, in situ hybridization or cytochemistry with antibodies, lectins or other probes for transcription factors, putative receptor proteins or their RNA message.

Olfaction: Neurotransmitters and Neuromodulators

- Identify the neurotransmitters, neuropeptides, receptors and second-messenger systems throughout the olfactory system.

- Identify the roles of olfactory axons in the developmental induction and maintained expression of neurotransmitters in postsynaptic, olfactory-bulb neurons.

- Evaluate the status of olfactory-bulb, dopamine neurons and their role in sensory disorders associated with Parkinson's disease.

- Determine the mechanisms underlying postsynaptic responses of neurons in central olfactory networks.
- Characterize the roles of neural activity and transmitter actions on gene expression in olfactory neural networks.
- Determine the neural circuits activated during different stages in the processing of olfactory, gustatory and tactile information to identify the influence of arousal and motivation on sensory perception, discrimination and learning.
- Develop mammalian olfactory-bulb, in vitro, slice and organotypic slice preparations to study membrane, biophysical properties, transmitter function and neural network, integrative functions.
- Employ electrophysiologic, recording techniques in anesthetized and free moving animal models to characterize neural-network function at all levels of the olfactory system.
- Develop "biologically realistic," neural-network-based, computational models for regions subserving the olfactory, gustatory and tactile sensations to identify mechanisms of sensory processing and learning.

Odor Perception and Cognitive Processes

- Evaluate the dynamics of olfactory adaptation, cross-adaptation and habituation.
- Investigate factors affecting odor recognition of complex mixtures.
- Identify the components of odor processing (recognition, identification, categorization, learning and recall) of different olfactory brain areas.
- Characterize the patterns of impairment in the processing and learning of sensory information in humans with neurodegenerative disorders that damage neurons in the chemosensory and tactile systems to elucidate the roles of those structures in sensory function and cognition.

Feedforward and Feedback Regulation of Olfactory Function

- Determine the functional importance of central feedback to the olfactory bulb in odor detection, recognition and learning.

Taste: Neurotransmitters and Neuromodulators

- Use biochemical and molecular probes to identify the neurotransmitters and receptors involved in the central processing of taste information.

- Determine the mechanisms underlying postsynaptic responses of neurons in central gustatory nuclei to neurotransmitters.

Central Representation of Taste Quality

- Use physiological and optical recording methods including voltage sensitive dyes to determine how taste quality is represented in the central nervous system.

- Develop computational and conceptual models of gustatory processing.

Neural Circuits Underlying Taste-Mediated Behavior

- Characterize neural circuits and neurotransmitters subserving taste-mediated ingestive, digestive and protective responses.

- Analyze the neural circuitry and neurotransmitter systems underlying conditioned flavor aversions.

- Analyze forebrain neural networks involved in gustatory processing to identify circuit organization, neurotransmitters and the physiologic principles of taste coding.

- Characterize the reorganization in the gustatory portion of the central nervous system after damage to the taste system by depletion or trauma.

Cognitive Processes in Touch

- Examine the role of cognitive processes in the perception of cutaneous and oral, tactile stimuli.

Active Perception in Smell, Taste and Touch

- Investigate active perception and purposeful sensation seeking in the chemical and tactile senses and contrast sensory effects from actively sought stimulation with passively imposed stimulation.

- Characterize the sensory elements associated with oral texture, temperature and viscosity.

- Investigate the chemically induced modulation of oral tactile sensations, including touch (e.g., astringency), temperature and pain.

- Explore how the properties and perception of mixtures of odorants, tastants, astringents and irritants relate to the properties and perception of unmixed stimuli.

Touch and Its Interaction With Other Senses

- Study interactions among the cutaneous senses, including touch, temperature, pain and itch at both the psychophysical and neurophysiological levels.

- Determine the anatomical, behavioral and physiological bases for interactions between the cutaneous senses and smell and taste.

- Develop models for shape perception, object identification and event perception that incorporate touch and kinesthetic information.

Plasticity, Including Development, Regeneration and Aging

Causal Role of the Olfactory Placode in Central Nervous System Development

- Identify the cellular and molecular factors that allow olfactory neurons to grow to and enter the central nervous system.

- Identify the factors by which incoming olfactory axons influence the mitotic cycle and differentiation pathways of olfactory-bulb precursor cells.

- Characterize the cellular and molecular mechanisms by which olfactory neurons induce and maintain the olfactory bulb.

- Characterize cellular and molecular features that distinguish olfactory glia from other glial cells.

- Develop organotypic and cell culture models to allow manipulative studies of early events in olfactory-system development.

- Develop genetically modified cell lines and transgenic animals to allow identification of factors and genes important for olfactory-system development.

Signals Controlling Olfactory-System Development

- Identify the cellular, molecular and genetic factors that regulate olfactory receptor cell neurogenesis, maturation, senescence and death.

- Identify transient and permanent cell contacts and molecular interactions among olfactory receptor cell axons and precursor cells, glial cells and neurons in the developing and adult olfactory bulb.

- Characterize trophic interactions among olfactory receptor neurons, the olfactory bulb and neurons comprising central olfactory pathways.

- Identify and characterize guidance-recognition mechanisms for migration, axon growth and synaptogenesis in the olfactory system.

- Locate, identify, and characterize segmentation and homeotic genes in olfactory development.

- Determine the role of immediate early genes and other transcriptional regulatory genes in olfactory-system development and plasticity.

- Determine the influence of hormones, neurotransmitters and peptides in olfactory-system development.

Primary Cell, Organotypic Cultures and Immortalized Cell Lines for Use in Understanding Olfactory Mechanisms and Neural Transplantation

- Develop further and use olfactory-neuroepithelium-derived, primary cell cultures to determine the factors that regulate mitosis of basal cells and the differentiation, survival and functional expression of receptor and transduction molecules.

- Develop and use organotypic slice cultures of the olfactory bulb and placode to characterize and manipulate the cells, molecules and genes that determine olfactory-system development.

- Investigate the ability of cultured olfactory neurons, glia and genetically transformed olfactory neuronal cell lines to enhance the growth-promoting microenvironment and to repair damaged pathways and circuits in the diseased or injured brain.

Aging and Cell Death in Olfactory and Gustatory Epithelia

- Study the pattern of gene expression preceding the death of olfactory receptor cells to identify the presence of "death genes" and the expression of genes that prolong viability.

- Determine the role of heat-shock and other proteins in the processes of cell death.

- Determine the integrity of calcium buffering and the activity of calcium-activated, proteolytic enzymes within olfactory neurons over the lifespan of the cell.

- Determine the trophic agents that support the olfactory receptor neurons and the normal sources of trophic support.

- Determine the role of macrophages and other immune-response elements in damage, healing and cellular replacement in the olfactory neuroepithelium.

Taste Bud Development and Turnover

- Identify the origin, diversity and lineage of taste receptor cells.

- Characterize the trophic influences in taste bud development and maintenance.
- Define the synaptic connectivity between taste buds.
- Study cell death and replacement of taste receptor cells.

Development of Electrophysiologic Responses to Taste Stimuli

- Examine the development of responses to lactose.
- Examine the development of taste responses, especially bitter responses, from the posterior one-third of the tongue during the postnatal period when taste buds in this region mature and accumulate.
- Determine whether species that have a behavioral preference for salt also have delayed physiologic development of salt taste.
- Assess the role of peripheral control of central taste circuits in development and during normal, taste-cell turnover and replacement.

Markers for Taste Cells *In Situ* and in Tissue Culture

- Develop markers for differentiated taste cells, including different types of taste cells.
- Use markers and improved culture techniques to determine the factors that regulate differentiation of taste cells.

Chemosensory Systems and Aging

- Explore the phenomenon of senescence in olfactory and gustatory systems to understand age-related chemosensory disorders.

Role of Experience and Touch

- Investigate the role of experience in altering tactile sensitivity and reorganization of the central nervous system.

Clinical Science Opportunities

The chemical senses and the tactile sense play important roles in experiencing chemical stimuli in the environment, including food and drink, pollutants, hazardous chemicals, warning signals such as smoke and the odorant additive to natural gas, and pleasurable fragrances. Impairment of the chemical senses in clinical disorders and normal aging can blunt or distort the appetite and impair the ability to detect smoke, leaking gas, toxicants and tainted foods.

Chemosensory disorders are responsible for thousands of patient visits every year, yet the actual incidence of chemosensory disorders in the population of the United States is unknown. The current estimate of the prevalence of chemosensory disorders is in excess of two million people. Furthermore, over half the population over 65 years of age exhibits olfactory impairment. The history of these disorders, including the age of onset and the duration should be fully explored. Epidemiologic information in this area is sorely needed. Essential to this effort is the comprehensive study of the incidence of chemosensory disorders which will address etiologic, geographic and occupational factors, aging and dementia, gender differences, cultural factors, environmental exposure, and genetic and socioeconomic factors.

The development of clinical tests of chemosensory function has lagged behind development of clinical testing of other sensory systems in one key area: testing the patient with techniques which do not require a verbal response on the part of the patient. Objective measures of sensory dysfunction are highly desirable in general and essential in some populations because some patients lack the ability to make complex verbal responses (e.g., infants, demented persons). Chemosensory evoked potentials and various brain imaging techniques (magnetic resonance imaging, positron emission tomography and computed tomography) show potential in this area and merit the investment of focused study.

Clinical chemosensory science has had recent advances in several key areas. The gene for Kallmann syndrome has been cloned, and the mechanism for olfactory dysfunction elucidated. Maternal ingestion of salt has been linked to high salt intake in the offspring in animal models. The extent to which salt preference and salt intake play a role in hypertension in humans requires further study. Chemosensory loss in Sjögren syndrome has been well described. Further study is in order to investigate the impact of local factors such as decreased salivary flow on chemosensory loss in this population.

Olfactory impairment in Alzheimer's disease has been demonstrated. Further research is needed to understand the underlying mechanisms and the pattern of functional loss. It is not yet known which olfactory tasks will signal dementia in the early stages of this disease and which will prove to be the best indicators of disease status as the progression unfolds.

Persons who age normally show impairment of the sense of smell that has impact upon their nutritional status, safety and quality of life. Their decreased ability to detect smoke or leaking gas place them at risk. Smell loss alters food choices in older persons to degrees that can be clinically significant. Many should decrease their intake of salt and sugar for health reasons, yet loss of enjoyment through decreased appreciation of food flavor seems to work against this goal. Losses in olfactory function appear to have a neurogenic basis in older persons. The degree to which life-long allergic rhinitis or chronic sinusitis contribute to or exacerbate the olfactory impairment in the elderly population warrants further study.

Genetic variation in sensitivity to chemical stimuli is clearly present in the population. Very little is yet understood. Modern molecular biologic techniques hold promise for understanding and ameliorating genetic chemosensory disorders.

The most common known causes of chemosensory disorders are nasal and paranasal sinus disease, head trauma, upper respiratory infections and allergic rhinitis. The actions of infectious agents and pollutants and the mechanisms by which they cause damage to chemosensory systems need to be explored. Current thrusts in the area of prevention and treatment include the use of prophylactic antibiotics and topically applied corticosteroids. Strategies for long-term management of chemosensory disorders need to be developed and communicated to health care professionals. Awareness should be increased to potential risk factors (detection of gas leaks and smoke), nutritional needs and compensatory adjustments to enhance the quality of life of persons who have these sensory impairments. A better understanding of chemosensory disorders and their causes should provide information which can be applied to strategies for prevention and treatment of chemosensory disorders.

Epidemiology of Smell, Taste and Touch Disorders

Etiology of Parosmia and Dysgeusia

- Determine the incidence, prevalence and risk factors of anosmia, hyposmia, parosmia, ageusia, hypogeusia, dysgeusia and hand/arm vibration syndrome and other tactile disorders.
- Determine the course of these disorders over time.
- Determine how the genes determining Kallmann syndrome alters chemosensory function.
- Investigate the genetic bases for chemosensory disorders.
- Determine the bases for idiopathic congenital anosmia.

Chemosensation in Systemic Diseases

- Find the cause for disorders of chemosensory sensitivity in systemic diseases.

- Identify the drugs that alter chemosensory perception either positively or negatively and determine their mechanism of action.
- Explore the extent and type of olfactory impairment in individuals with AIDS dementia complex and determine the degree of central and peripheral involvement.
- Determine the pattern and extent of olfactory loss in Alzheimer's disease and related dementias, their association with underlying neuropathology and the prognosis for recovery.
- Investigate the functional lateralization of olfactory processing.
- Investigate the consequences of high maternal salt intake on offspring's salt intake, salt-taste sensitivity and salt preference and the relation to blood pressure in humans.
- Determine how inflammation occurring in the olfactory cleft affects olfactory tissue.
- Determine whether inflammation can lead to irreversible impairment of smell, taste and touch.
- Investigate longitudinally the contributions of lifelong nasal allergy, inflammation, chronic sinusitis and exposure to environmental agents on olfactory sensitivity in the elderly.

Development of Diagnostic Tests

- Develop diagnostic methods for specific smell and taste disorders.
- Improve the objectivity of psychophysical measures, eliminating the need for verbal responses by the subject.
- Develop new instrumentation for monitoring the time course of chemosensory disorders.
- Evaluate evoked potentials and electrogustometry for clinical diagnosis.
- Devise chemosensory-based diagnostic strategies to differentiate among types (cortical or subcortical) of dementias, for example, Alzheimer's or AIDS-related, which have associated olfactory impairments.
- Develop molecular probes that may be of prognostic value in evaluating persons with chemosensory disorders.
- Explore the use of advanced brain imaging techniques (such as computed tomography and magnetic resonance imaging) in the diagnosis of smell, taste and touch disorders.

- Identify markers in, or physical parameters of, body fluids or secretions that provide corroborative diagnostic indicators of chemosensory dysfunction.

Genetic Variation

- Study the impact of genetic variation on perceptions of odorants and tastants.

Olfactory Pathology

- Evaluate the potential use of biophysical, biochemical, molecular biological and immunobiochemical studies of biopsy material to diagnose olfactory disorders.

- Determine whether immortalized cell lines can be produced from olfactory neuroepithelial biopsies or fetal material and evaluate, in animal models for future potential human explants, whether genetically altered olfactory-cell lines might be useful for treating various central nervous system diseases.

Gustatory Pathology

- Relate lingual and mucosal lesions to taste disorders.

- Identify, survey and study human populations at risk for loss of the sense of taste.

- Identify those drugs reported to alter the sense of taste and validate the effects under controlled studies.

Animal Models

- Develop animal models for the study of chemosensory deficits and excessive intake of nutrients such as sodium that is mediated by taste.

- Test the effects of drugs on behaviors mediated by smell and taste in animals.

Diagnosis of Touch and Related Disorders

- Develop devices and techniques for testing the facial and oral sensitivity of individuals without taste disorders and those with taste disorders.

Lifespan Development of Sensory and Affective Response

- Determine how dietary and environmental odorant and tastant exposure modulate sensitivity and affective responses to these stimuli and impact on nutrition.

- Evaluate chemosensory sensitivity in infants and young children by means of new techniques that are sufficiently sensitive to serve as effective clinical procedures.

- Determine the role of chemosensory stimuli in human social and sexual behavior and reproductive function.

- Determine how changes in affective responses to chemical signals influence patients' prognoses.
- Examine how olfactory and gustatory sensitivity vary over time in the same individual.
- Examine individual differences in olfactory sensitivity and seek predictors and correlates of high and low sensitivity.
- Encourage the development of standardized measures of touch sensitivity suitable for infants and throughout development.

Aging

- Study the reasons for variability in the chemosensory performance of the growing elderly population.
- Determine whether the lesions responsible for the olfactory loss in the elderly are in the neuroepithelium or the central olfactory pathways or both.
- Assess the effect of the health status of the elderly on their chemosensory function.
- Study the effects of aging on touch sensitivity and activities related to touch.

Impact of Chemosensory Disorders on Nutrition, Safety and the Quality of Life

- Evaluate risks associated with nutritional factors in individuals with chemosensory disorders.
- Identify strategies to prevent and manage the adverse psychological effects of chemosensory dysfunction.
- Determine how chemosensory stimuli act to modulate digestion and utilization of nutrients and whether chemosensory disorders compromise these processes.
- Investigate the interaction between chemosensation and the opioid system.
- Assess the influence of a covert decline in chemosensory function on safety in the home and workplace.

Effects of Occupational, Environmental and Infectious Agents on Function of Smell, Taste and Touch

- Develop detectors to protect specific employee populations, such as fire fighters, police, special hazard teams and astronauts.
- Investigate olfactory function in individuals from regions of the country where there is a high concentration of industrial or agricultural toxicants.

- Assess the role of pollution and occupational exposure on chemosensory function.
- Identify odorants that modify mood, performance and behavior and determine their mechanisms of action.
- Investigate whether individuals with multiple chemical sensitivities have altered chemical senses.
- Protect and monitor the worker for incipient chemosensory losses attributed to exposure to the occupational environment.
- Investigate the role of the olfactory nerve in the transport of toxins and pathogens to the brain.
- Study the potential of the olfactory nerve for administration of pharmacologically relevant substances to the brain.
- Develop animal models to investigate these processes.
- Examine the environmental and occupational agents that may affect touch.
- Develop diagnostic tests to determine both normal and abnormal touch sensitivity.

Strategies for the Management of Sensory Disorders, Including Prevention, Treatment and Rehabilitation

Prevention of Chemosensory Disorders

- Develop new means of preventing chemosensory losses.
- Examine the unintended consequences of medical and surgical therapy on chemosensory function.

Treatment Strategies for Smell, Taste and Touch Disorders

Smell and Taste Disorders

- Design and implement clinical trials of therapeutic strategies for sensorineural disorders of smell and taste.
- Develop diagnostic and therapeutic approaches to chemosensory dysfunction that use advances from molecular biologic, cell and fetal tissue research.
- Develop tests for the prenatal diagnosis of Kallmann syndrome.
- Evaluate strategies, including gene therapy, for the prevention and treatment of Kallmann syndrome.

- Create transgenic models to study the basis of olfactory development.
- Map the chromosomal localization of various olfactory genes to determine whether cross sensory modality gene proximity is a general phenomenon that will facilitate the cloning of other genes for hereditary defects and provide diagnostic reagents.
- Develop clinical intervention protocols for genetic intervention in individuals with Kallmann syndrome.
- Identify other genetic defects that affect the smell and taste functions.

Touch Disorders

- Investigate the relationship between changes in touch and changes in object manipulation and object identification in populations with diminution of touch sensitivity.
- Develop practical, compact devices to present controlled, complex patterns to the skin.
- Use imaging techniques to measure central nervous system responses to cutaneous stimuli.

Tactile Aids

- Encourage cooperative investigations of tactile aids involving rehabilitative specialists, otolaryngologists, engineers, speech scientists and sensory scientists.

Voice and Voice Disorders

The vocal folds in the larynx (voice box) separate during breathing so that air can enter the lungs. During swallowing, the vocal folds are forced tightly together to prevent food or liquid from entering the lungs. For coughing, which is a protective reflex action, the vocal folds seal tightly and then separate abruptly. Voice or phonation is produced when airflow from the lungs causes the vocal folds to vibrate. The vibration of the vocal folds is the sounding source, and the sound is further modified by actions of structures within the throat, nose and mouth. When vocal fold vibration is impaired, sound generation for voice, speech and singing is affected. A wide variety of voice disorders occur, some for structural, neural or behavioral reasons.

Voice science is a rapidly growing field. Within the last decade, the field has expanded in a variety of ways. A large, new knowledge base and clinical delivery system have developed, resulting in recognition, diagnosis and treatment of patients with voice impairments, laryngeal pathology and swallowing disorders.

New technologies for voice science have been developed. These technologies have enabled improved visualization of various components of the voice production mechanism, particularly the larynx. They have also opened new vistas on the functioning of the vocal folds and are leading to the development of new theoretical models of laryngeal behavior. Such technologic improvements are also providing new databases of value in understanding, evaluating and treating individuals with voice or swallowing disorders.

Newly developed measures of voice can be used to evaluate the efficacy of existing therapy and suggest possibilities for future improvements. New surgical techniques called phonosurgery are being used to improve and restore voice by removing benign growths, correcting structural abnormalities and repairing trauma. Promising new treatments have emerged, including the use of botulinum toxin in spasmodic dysphonia.

Major Basic and Clinical Research Opportunities

Normal Structure and Function

Respiratory, Laryngeal and Upper Aerodigestive Tract Physiology

- Study the nature of respiratory, laryngeal and upper aerodigestive tract actions and interactions in voice production and determine the principles that govern adaptive and maladaptive behaviors in response to laryngeal disorders or diseases.
- Gather data on voice production that encompass various domains, including neural, muscular, structural, aeromechanical, acoustical and perceptual domains.
- Conduct research to delineate further the effects of bolus characteristics, respiratory parameters and voluntary control on timing and extent of laryngeal elevation and closure and pharyngeal contraction during swallowing.
- Conduct studies on the mechanisms involved in the control of vocal pitch, loudness, quality and register, including mechanisms associated with singing.
- Study the role of sensation, including hearing, vibrotactile sensation, proprioception and respiratory cues, in the development and use of voice in normal, impaired and exceptional subjects.
- Delineate the acoustic to perceptual transformation in voice-quality disorders, with special attention to those aspects of the voice signal that give rise to the perception of disorder and its quantities.

- Study the timing mechanisms of laryngeal behavior in coordination with respiratory and articulatory activity.
- Conduct studies on the exceptional (trained) singer to specify the limits of the human voice and its optimal efficiency.
- Determine the effects of lifestyle choices (diet, smoking, drug use, exercise and alcohol consumption) on the function of the larynx and upper aerodigestive tract.

Neural and Vascular Mechanisms

- Conduct studies of neural control of the larynx for voice production, respiration and swallowing in humans and animals, including the elucidation of reflex mechanisms for each.
- Use transcranial magnetic stimulation and sensory evoked potentials to map cortical areas pertinent to laryngeal function.
- Determine the activity of the brain stem motoneuron pool during different phases of respiration, phonation and swallowing via the use of short- and long-latency reflexes elicited through electrical stimulation of the recurrent laryngeal nerves.
- Obtain information concerning the function of neural sensors in the control of voice production.
- Determine the similarities and differences in human laryngeal physiology to that of other species proposed as models for human voice production and swallowing.
- Use electrically or chemically elicited phonation from the periaqueductal gray area of the midbrain in anesthetized animals to study the behavior of laryngeal motoneurons, sensory afferents of the larynx and mechanisms of phonatory control.
- Conduct studies of blood circulation and its autonomic control to laryngeal tissues and the relations to biomechanical changes in the larynx, vocal fatigue and laryngeal lesions.

Biomechanics

- Develop common spatial and relational references for laryngeal function to make it possible to gather multivariate data to enhance the modeling of laryngeal function and dysfunction.
- Determine the importance of lubricating fluids on the vibratory function of the vocal folds and study the composition and aberrations in these fluids.
- Conduct studies of the material properties and biomechanical behaviors of laryngeal structures.

- Determine the physiologic consequences of muscular atrophy of the upper aerodigestive tract on vocalization, swallowing and respiratory function.

Development and Aging

- Conduct studies of the mechanisms of epithelial-mesenchymal tissue interactions that are a driving force in the normal development of the larynx and its final form.
- Specify the nature of voice production as it relates to the developing structure of the entire respiratory system, upper aerodigestive tract and larynx in particular.
- Obtain data on laryngeal and upper aerodigestive function of normal octogenarians, nonagenarians and centenarians for voice production and swallowing.

Cellular and Molecular Biology and Anatomy

- Specify the sites of hormonal influence on the respiratory system, upper aerodigestive tract and larynx in particular, as well as hormonally affected changes in voice production.
- Determine the biochemical and structural specializations characteristic of laryngeal muscle fibers and their innervation.
- Define the distribution of extracellular matrix molecules, oncogene expression, growth factors and growth-factor receptors as they relate to normal structure of the aging larynx.
- Conduct studies of the cellular biology of cartilage and joint deterioration in the larynx as they affect voice production and swallowing in aging.

Diseases and Disorders of the Larynx and Upper Aerodigestive Tract

Epidemiology and Prevention

- Gather data on the incidence and prevalence of voice and swallowing disorders.
- Conduct epidemiological surveys of the influence of external environmental factors on voice production to identify important agents and clarify pathophysiology and develop strategies for prevention, diagnosis and management of the resultant voice disorders.
- Identify genetic and environmental causes of congenital disorders of the larynx and pharynx.
- Develop strategies for prevention and early detection of cancer of the upper aerodigestive tract.

- **Conduct epidemiologic and case-control studies to identify factors which may lead to focal dystonias of the head and neck.**

Pathophysiology and Potential for Improved Therapy

- **Improve the understanding of infectious and allergic disorders of the upper aerodigestive tract and develop better therapy.**
- **Identify and study genetic influences on laryngeal function and dysfunction.**
- **Obtain information on the effects of drugs (alone or in combination with other therapy) on the voice.**
- **Study the role of psychogenic factors in the pathogenesis of voice disorders and response to treatment and develop criteria for distinguishing psychogenic from organic voice disorders.**
- **Determine the role of extra-cellular matrix, growth factors and oncogenes in wound healing of the larynx and in the pathogenesis of laryngeal and tracheal stenosis.**
- **Determine reasons for gender differences in susceptibility to vocal disorders.**
- **Study the effects of aging on voice production to establish the true nature of age-related voice (not pathologic) changes and develop treatment to forestall or prevent such changes.**
- **Study the effects of respiratory disorders on the voice.**
- **Conduct studies of recurrent laryngeal nerve regeneration as well as denervated laryngeal muscles to improve the understanding of pathogenesis and treatment of laryngeal paralysis.**

Evaluation of Current Therapy

- **Conduct prospective, controlled trials to assess effectiveness of treatment for voice disorders, including phonosurgical procedures and voice therapy.**
- **Conduct long-term, large-scale studies of the management of laryngeal papillomata to address recurrence rates, effects of treatments, effects of cofactors and rates of association with carcinoma of the larynx.**
- **Evaluate prospectively the effects of conservation surgery for upper aerodigestive tract malignancy on speech, swallowing and breathing.**
- **Determine the effects of irradiation and chemotherapy on laryngeal function.**
- **Conduct prospective trials to develop criteria to predict optimal dosage and placement of botulinum toxin injection in the management**

of focal dystonias and to determine the long-term effects of this therapy.

- Characterize the diffusion of botulinum toxin in tissues and determine whether retrograde transport to the brain stem accounts for some of the substance's therapeutic actions.

- Conduct studies of the effects of acid and alkaline gastroesophageal reflux on voice and swallowing and evaluate the efficacy of treatment for these disorders.

Technology

- Use simulation modeling to predict the effect of modifying individual elements controlling laryngeal function and account for the effects of surface tension, other tissue surface properties and the specific effects of muscle contractions, including nonlinear phenomena.

- Use magnetic resonance imaging and positron emission tomography to seek structural lesions in the central nervous system in patients with voice and swallowing disorders and to improve understanding of the control of the upper aerodigestive tract.

Diagnosis

- Conduct studies on large populations of normal and disordered speakers to clarify the relations between quantitative measures and perceptual vocal characteristics to determine how to use quantitative measures in making treatment decisions.

- Determine the usefulness of aeromechanical measurements in the differential diagnosis and assessment of treatments for vocal disorders and evaluate the contribution of the respiratory system to aerodynamic measures.

- Develop meaningful parameters to evaluate quantitatively laryngeal visual images.

- Study the impact on laryngeal electromyography of variations in electrode configuration, interaction of electrodes with muscles, techniques used to verify electrode placement and testing protocols.

- Develop techniques for nonvoluntary activation of laryngeal nerves as a means of verifying the integrity of laryngeal nerves in uncooperative or anesthetized patients.

Treatment

- Conduct studies of electrical pacing of the larynx to evaluate the procedure and determine its long-term efficacy.

- Develop prosthetic speech instruments which mimic natural voice characteristics and express paralinguistic features of stress, intonation and juncture.

o Develop and determine the usefulness of techniques for intra-operative monitoring and assessment of vocal function in improving surgical results and preventing complications.

Speech and Speech Disorders

Speech Production and its Disorders

Spoken language is the most distinct human faculty. Although humans can communicate in a variety of ways, including manual gestures and written alphabets, speech is the most common means of language expression in humans. One of the most important milestones in child development is the emergence of language. Research on speech and its disorders offers a better understanding of how speech develops, how it is maintained through the lifespan, and how it is impaired by disease, trauma and other factors. An ultimate goal is to improve the assessment and management of speech disorders in children and adults.

The great majority of children acquire speech naturally and easily to take their place in the community of native speakers of a language. But about ten percent of children experience difficulties in acquiring speech. Sometimes the source of difficulty is known, for example, a hearing loss, a cleft palate or other craniofacial anomaly, or damage to the nervous system. However, many children have speech impairments for which the cause is unknown. Included in this category of idiopathic speech disorders are stuttering and most phonological (speech sound) disorders or sound learning. Some children learn English as a second language and may have difficulty in acquiring a phonological system that is different from the first one they learned. Furthermore, a child learning a second language may have a phonological disorder, so the ordinary difficulties in learning a nonnative language are compounded by a fundamental impairment in the systems that support phonological learning.

Speech disorders have adverse effects on a child's educational achievement, emotional well being and social participation. Some speech disorders in children can be treated fairly effectively, others require a substantial intervention effort, and for others, there is no consensus on the management of choice. For some speech disorders, preventative measures are known, but for others, such as the idiopathic disorders, the steps to prevention are unclear.

Speech disorders in adults can be the outgrowth of speech impairments in childhood or they can be acquired subsequent to the development of speech. Included in the latter category are acquired disorders related to adult-onset hearing loss, accidental trauma, ablative surgery or diseases of the nervous system. Moreover, some adults with reading or writing difficulties had phonological or other speech disorders during childhood. It is possible that some proportion of reading or writing difficulties in older children and adults are rooted in earlier problems in phonological development. Speech disorders in adults can greatly limit occupational opportunities and advancement, human interaction, overall quality of life and social activities.

Research on speech and its disorders has brought new understanding to many issues. Technological advances have profoundly affected the ways investigators can study speech production and the various disorders that impair its component processes. As recently as a decade ago, it was a significant accomplishment to collect acoustic or physiologic data for brief samples of speech from only five to ten subjects. Modern technology permits scientists to record and analyze data in long speech samples recorded from large numbers of subjects. Moreover, many of the analyses performed in the laboratory have become available to the clinician, especially through the use of computers. As the knowledge base on speech production has grown, so has the understanding of its basic processes and its susceptibility to disruption. Research on speech production also has been vitalized by increasing efforts to apply knowledge from various fields, including psychology, linguistics, engineering, neuroscience, computer science, genetics and a number of biomedical specialties.

Basic Structure and Function

- Study vocal tract morphology and dynamics in large numbers of subjects and use the data to develop articulatory models.
- Study cell structural and functional properties to understand better the characteristics of orofacial muscle tissue in health and disease.
- Examine the sensory mechanisms associated with the orofacial region from the structural, physiological and psychophysical perspectives.
- Study the neural mechanisms underlying voluntary control of orofacial structures in experimental animals.
- Study the coordination among speech articulators and subsystems by simultaneously collecting data on articulatory, laryngeal and respiratory events during speech, and use the resulting evidence to develop comprehensive models of speech movement control.
- Study human central nervous system function in relation to speech production using available noninvasive procedures.

Lifespan Studies

- Use refined perceptual, acoustic or physiologic techniques to investigate the detailed changes that occur in the vocalizations of typically developing infants. The resulting data are necessary for understanding normal speech development and interpreting similar data from infants judged to be at risk for speech disorders.
- Compare the vocal development of infants raised in different language backgrounds to determine the timing and nature of language-background influences on speech development.
- Collect detailed data on the vocal development of infants judged to be at risk for speech disorders.
- Identify the bases and underlying control principles for orofacial, laryngeal and respiratory actions as infants make the transition from babbling to first words.
- Study various aspects of speech production from infancy through childhood. Data on developmental changes in acoustic, aerodynamic, kinematic and linguistic properties should be incorporated in developmental models of speech production.
- Describe how advances in spoken language during normal development are associated with changes in motor control of speech.
- Develop for males and females normative databases for acoustic, aerodynamic and kinematic measures of speech production from infancy through the advanced years.
- Use imaging methods to study developmental changes in vocal tract anatomy in order to assemble a vocal tract atlas for males and females of different ages.
- Determine the biomechanical accompaniments of growth, maturation and senescence in the speech production system.
- Determine, throughout the lifespan, the effects of toxic exposure, mechanical trauma, and neurogenic damage to the tissues of the speech production system.
- Examine in detail changes across the lifespan in performance characteristics of the speech articulators, such as speed, acceleration, range of motion, strength, fatigability and also pressure and phonatory regulation in both speech and nonspeech oromotor tasks.
- Extend earlier studies of speech motor control and phonological performance to a more ecologically valid body of utterances, for example, real single words spoken

spontaneously and utterances that are sufficiently long and complex to stress memory and cognition.

- Elucidate changes across the lifespan in extent and magnitude of coproduction (coarticulation) of phonetic segments within larger units of speech (words or phrases) and relate these changes, where possible, to changes in the perceptual representation of the lexicon.
- Account for the slowing of articulation observed in elderly populations in terms of neurogenic and muscular changes.

Modeling

- Continue to develop theories of speech production processes that incorporate new theoretical developments from related disciplines.
- Develop and evaluate models for individual components and subsystems of speech production. Because the entire system of speech represents complex anatomy and physiology, progress will depend on an increased understanding of the system's various parts.
- Develop and evaluate physiologic and acoustic models of speech production that can be applied to a wide range of issues in normal and disordered speech.
- Continue efforts to solve the one-to-many relation between acoustic signal and vocal tract configuration, and evaluate progress with a diverse population of speakers.
- Attempt to use new information about central nervous system functioning (brain imaging) to propose new models of neural control of speech and other behaviors using the same musculature.
- Extend or apply recent advances in linguistics, information processing, communication engineering, artificial intelligence and allied fields to problems in speech production and perception.
- Modify existing models of speech production to extend their relevance to a broad population of speakers (both genders, various ages and of diverse physical sizes).

Technology

- Foster the development of new technological systems for the acoustic and physiologic study of speech. The need is especially great for systems that can be used with speakers of either sex and of varying ages.
- Evaluate existing technological systems and measures to determine their validity, reliability and efficiency. A number of

quantitative indices are now available for the study of speech and its disorders, but the relative merits of these measures have not been systematically evaluated.

- Continue to develop and evaluate noninvasive procedures for imaging the vocal tract and monitoring movements of the speech structures.
- Improve the capability for the simultaneous monitoring of respiratory, laryngeal and articulatory events in speech production. This technological capability is critical to the understanding of interactions among the components of speech production.
- Apply brain imaging techniques to the study of the neural events associated with various tasks of speech production and perception.
- Continue developing technological systems for speech synthesis of various types. Terminal analog synthesis has been highly successful in generating speech stimuli for perceptual experiments and other purposes, but refinements are needed to make synthesis systems flexible and easy to use. Articulatory synthesizers are needed to model the relationship between structural movement and acoustic output.
- Develop and apply procedures of machine speech recognition for a diverse population of speakers, including children, men, women and speakers who differ in speaking rate, dialect, disorders or other features.
- Explore the clinical application of speech synthesis and speech recognition devices, including their incorporation into augmentative and assistive systems for those with severe speech impairments, as well as for the development of well-defined strategies for assessment and intervention.
- Develop and evaluate algorithms and procedures to study the relationship between perceptual ratings of speech and various acoustic and physiologic measures of speech activity.
- Refine computer-based methods for the collection of phonetic and phonologic data, which may be coordinated with acoustic or physiologic analyses.
- Explore the application of expert systems to the assessment and management of various speech disorders (i.e., toward improvements in augmentative and assistive systems).

Disorders of Speech Production

Structurally Based Disorders

Acquired Defects

- Optimize treatment outcome through more consistent documentation of speech production skills in the premorbid state, postablative state and posttreatment state, with longitudinal study of stability of treatment results. (Although innovations in surgical and prosthetic treatment are reported on a continual basis, relatively few of the reports contain adequate documentation of speech production. In many reports, assessments consist solely of global judgments).

- Evaluate the interaction of treatment with all possible concomitant areas of deficit including hearing, cognitive status and language.

- Foster development of standardized assessment protocols.

- Develop treatment efficacy data, including comparative cost-benefit data on both physical management (surgical and prosthetic) and speech treatment.

Congenital Anomalies

- Expand the knowledge base regarding prevalence of specific types of communication disorders in multiple anomaly syndromes. The purpose is to prepare clinicians and families to deal with expected areas of deficit in individuals with known syndromes; and conversely, to add to the phenotypic spectrum of recognized syndromes so that diagnosed communication disorders may be used as possible indications of the presence of these syndromes. This effort must take into account both individual variation and the range of syndromic expression.

- Expand the database regarding development of infants with congenital anomalies, with specific emphasis on prelinguistic development, early differences in communication development (including response to treatment) and long-term development (including stability of results).

- Encourage continued research into the use of instruments such as the electropalatograph to improve the efficiency of articulation therapy.

- Encourage research on the effects of early versus late intervention and coordinated interdisciplinary team care versus compartmentalized care.

- Develop longitudinal and cross-sectional data regarding response to treatment in individuals who are from developing countries and who have untreated or inadequately treated cleft palates. Specific areas of concern include compliance with treatment recommendations and acquisition of a new phonological system (English) with an "altered" speech production mechanism (repaired velopharyngeal system).

Neurogenic Disorders of Speech and Oral Motor Function

Motor Speech Disorders

- Develop standardized assessment profiles for neurogenic disorders, based on perceptual, acoustic, physiologic and psychosocial data, which, taken together, will provide a firm basis for understanding impaired functions including respiration, phonation and articulation.
- Determine how motor speech disorders are affected by individual characteristics such as age, gender, general health and psychological status.
- Examine the relationship among various aspects of the disorders, including the relationship between respiratory function and oral articulatory precision in individuals with various types and severity of motor speech disorders.
- Study task and instructional variables that affect speech performance of individuals with a variety of disorders and at various stages of progression of the disorder.
- Investigate the quality and severity of speech motor impairments that often accompany conditions such as aphasia, dementia, traumatic brain injury and affective or other psychiatric disorders.
- Study changes in speech performance longitudinally in individuals who are either recovering from or experiencing progression of motor speech impairment.
- Examine the abilities and strategies of individuals to compensate for motor speech impairment.
- Examine variables related to listeners' perception of dysarthric speech and the influence of listener variables and characteristics on judgments of speech intelligibility.
- Assess the impact of motor speech disorders on the psychosocial function and quality of life of individuals who experience these disorders.
- Compile normative data related to aging and speech production.
- Investigate the use of computer recognition of dysarthric speech with the goal of automatic recoding and synthetic output.

- Study the relationship between perceptual ratings of speech abnormality and measures of the acoustic and physiologic events of speech.
- Assess orofacial sensory function and speech perception in individuals with dysarthria.
- Study the efficacy of various interventions for dysarthria and the factors that contribute to candidacy for such intervention.

Swallowing Disorders

- Evaluate changes in the pattern and severity of swallowing disorders over time in individuals with either progressive or diminishing swallowing disorders of various causes.
- Examine functional swallowing abilities in individuals with various types and severities of swallowing disorders and relate these functional outcomes to the nature and extent of the underlying pathophysiology.
- Examine the mechanism of aspiration pneumonia and variables that relate to its occurrence so that data related to aspiration can be used in "at risk" equations.
- Study the relationship between pharyngeal and esophageal function in individuals with various types and severities of swallowing disorders.
- Develop improved assessment protocols, drawing on available methods such as videofluorography, manometry, electroglottography and ultrasound imaging.
- Study orofacial sensory function and respiratory function in individuals with swallowing disorders.
- Study the population of elderly and institutionalized individuals at risk for swallowing disorders and determine the consequent nutritional and medical problems.
- Study multicultural considerations relating to dysphagia treatment, such as dietary habits and proscriptions.
- Study the efficacy of various interventions for swallowing disorders and the factors that contribute to candidacy for such intervention.
- Investigate the effects of swallowing disorders on speech functions.

Stuttering

Onset and Development of Stuttering

- **Study the onset and development of speech dysfluency in nonstuttering children, particularly between two and six years of age.**
- **Study the parallel development of speech dysfluency, phonology, expressive and receptive language and cognitive development in children who stutter and those who do not, particularly between two and six years of age.**
- **Study the relationships among intelligibility, phonological processes, articulation errors and speech dysfluencies in children who do and do not stutter.**
- **Study sources of acoustic, physiologic, perceptual and behavioral heterogeneity among children who stutter, as a prelude to the objective assessment of subgroups, behaviorally and etiologically.**
- **Study the relationship between overt repairs, covert repairs, speech errors and speech dysfluencies in young stutterers and nonstutterers' conversational speech.**
- **Study the relationship between speaker and listener speaking rate, response time latency and simultalking (listener's speech overlapping in time with speaker's speech) and speech dysfluency in stutterers and nonstutterers.**
- **Study mothers' and fathers' nonspeech behavior in association with their children's dysfluent speech, particularly the time course of parent and child nonspeech behaviors during the child's fluent and stuttered speech.**
- **Study the nonspeech behavior as a possible indicator of the child's development of awareness of speech behavior and errors in this behavior.**

Speech Production and Related Issues

- **Examine the number and nature of subtle aberrations speech production, particularly as they may relate to behavioral symptoms and risk factors for continued stuttering in children.**
- **Study tremor as it may manifest itself in respiratory, phonatory and articulatory structures and muscles, particularly as it relates to the onset, development and occurrence of stuttering in children.**
- **Study the number, nature and time course of speech production events associated with instances of stuttering in children and adults.**

- Study the relationship between stuttering, self-reporting of anxiety, autonomic arousal and other nervous system functions.

- Study the relationship between simple and complex manual and speech timing tasks, autonomic arousal and disruptions in rate, precision and sequencing of these tasks.

- Study the possible genetic transmission or inherited predisposition for stuttering, in individuals exhibiting a stuttering phenotype which is based on objective, well-defined and replicable criteria.

Diagnosis and Treatment

- Study the treatment efficacy of standard therapeutic regimens on changes in stuttering as well as relapse in changed stuttering in children with and without concomitant communication problems such as expressive language disorders or delays.

- Study the naturalness of speech behavior associated with changes in speech fluency that result from various standard therapeutic regimens.

- Study children who stutter for acoustic, physiologic and behavioral events, including age of onset, that indicate that the child may be at risk for continued, chronic stuttering.

- Study the effects of time-out procedures on experimenter's or clinician's speech rate, length and complexity of utterance, response time latency and any associated change in stuttering.

Related Issues

- Assess differences between those who stutter and nonstutterers in biochemical parameters including serum levels of cations (magnesium) that may affect neurotransmission during nonspeech and speech tasks.

- Study the onset, development, number and nature of symptoms associated with acquired stuttering and compare them with similar events associated with developmental stuttering.

- Study the acoustic, physiologic and behavioral characteristics of stuttering-related phenomena such as word retrieval difficulties and develop explanatory models to account for similarities and differences between stuttering and such phenomena.

- Study the influence of frequency and accuracy of self-detection of speech errors on ongoing speech fluency. This information should be useful in the development of models of dysfluency. General studies are needed on the speech perception abilities of children and adults who stutter.

- Encourage improved perceptual as well as automated means for identifying stuttering, classifying people who stutter, and reliably and validly determining risk factors for continuing stuttering.

Articulation and Phonological Disorders

- Identify possible sources and domains of disruption in the sound system of language, with broad and interdisciplinary examination of the linguistic, cognitive, motoric, perceptual, neurogenic, genetic and biologic bases of the disorder.
- Delineate potential subgroups of phonological disorders with appropriate techniques for the differential diagnosis and effective treatment of these populations.
- Extend the study of phonology and phonological disorders to encompass a speaker's entire lifespan.
- Determine cross-linguistic acquisition and organization of sound systems to use as a baseline for the diagnosis and treatment of disorders, and also determine the range of normal variation in the development of linguistic systems.
- Isolate the basic units of phonologic systems, determine their nature (acoustic and articulatory) and characterize how they may change with development.
- Obtain more complete information about components of developing phonologic systems that may be susceptible to disruption, including potential disturbances in the acquisition of vowels, suprasegmentals and sound changes associated with morphology.
- Develop, evaluate and standardize phonologic assessment procedures based upon current theoretical models of speech production, speech perception and cognitive development.
- Promote improvements in the treatment and monitoring of phonological disorders, particularly in children from multicultural populations.
- Encourage the clinical evaluation of theoretically motivated treatment paradigms within a developmental perspective, including clinical trials with children who may have different patterns of sound disorders.
- Explore the possible utility and effectiveness of treatment paradigms across populations,

including second language learners and persons with hearing impairments.

- Track the long-term efficacy of phonological treatment and identify potential factors that may contribute to regressions in learning or lack of retention over time.
- Study the relationships among child head injury, school failure and speech disorders.
- Evaluate the social, educational and employment consequences of phonological disorders. Include the possible associative relationships to lack of or not completing education, unemployment, delinquency and dialect, throughout the lifespan using retrospective and prospective studies.
- Foster investigations of the acoustic-phonetic evaluation of speech in children that relies on characteristics of the developing vocal tract.
- Characterize further the acceptable range of variation in development of acoustic-phonetic properties of normal speech in children.
- Define the relationship between phonological development and other linguistic skills, such as reading and writing.
- Study the occurrence and type of speech articulation disorders in populations with neural and genetic deficits, such as cerebral palsy or mental retardation.
- Explore the relationship between disorders of speech and language, including phonology and its concurrence with voice, expressive language and hearing impairment.
- Isolate the range of factors contributing to intelligibility of phonologically impaired speech and explore applications to speech synthesis and recognition.
- Establish criteria for differentiating clinically relevant phonological and articulatory variation from normal language differences across cultural groups.
- Extend and enrich the existing descriptions of the acquisition of English phonology. Accounts of phonological development will chart the orderly additions to and changes in the inventory of phonetic and phonemic (contrastive) sound units, as well as changes in or additions to processes and rules that operate on words and smaller linguistic units.
- Extend existing work on English to nonstandard dialects of American English and to other languages that are spoken in the United States.

- Determine the relationship between phonological acquisition and other aspects of linguistic and cognitive development.

- Determine what role early bilingualism plays in the rate of acquisition and eventual adequacy of phonological control of the native language and chart changes in the individual's ability to master the production of second dialects and languages throughout the lifespan.

- Assess the perceptual consequences, for example, decrease in intelligibility of various divergences from the norms of standard English, such as application of phonological processes or inventory limitations, both typical and atypical. Such work should target the speech of children learning English as a native language, as well as individuals of various ages who are acquiring English as a second language.

Speech of People Who are Hearing Impaired

- Conduct studies of the effects on speech production of hearing loss at different stages of life.

- Delineate the speech production potential and hearing status of hearing-impaired infants and young children, noting the differences that might occur in children who are hearing-impaired from birth versus those acquiring a hearing loss later in life.

- Investigate the speech production characteristics of children with various degrees of hearing impairment, including mild, moderate and severe hearing losses. Data from such studies may serve as population-typical data predicting speech performance in young children who are hearing-impaired. They may also serve as benchmark performance measures for children using assistive listening devices, such as tactile aids, hearing aids or cochlear implants.

- Improve speech training aids to deliver articulatory information in a well defined manner and to assess learning independently for different components of the articulatory system.

- Examine the effects of the techniques used to train speech production skills in persons who are hearing impaired.

- Investigate the change over time in the influence of tactile aids, analog and digital hearing aids and cochlear implants on speech production in children and adults.

- Examine the speaker-listener interactions involved in communication with speakers who are hearing impaired.

- Explore the speech production characteristics of adult speakers with sustained hearing impairments after speech is developed, adults with intelligible speech but longstanding hearing losses and adult users of cochlear implants.
- Investigate factors that cause major effects on the intelligibility of the speech of individuals who are hearing impaired as a function of educational history, residual hearing and communication mode.
- Develop methods to improve overall speech intelligibility in individuals with various degrees of hearing loss.
- Explore intervention strategies for developing intelligible speech for interested individuals who are hearing impaired using either predominantly oral systems or combinations of communication systems.

Augmentative and Assistive Systems

- Conduct real-world studies of the characteristics of clinical populations who use augmentative communication, their interaction with existing devices and unmet needs. The results of such studies should guide device development.
- Study the demands in using augmentative devices, including cognition, literacy, linguistic and pragmatic function requirements of successful use. An understanding of these demands will lead to appropriate device selection as well as to the development of suitable training regimes. It is important to address the development of skills needed to use these devices as well as the variations in device performance in different conditions.
- Study the integration of natural speech with the use of augmentative communication devices.
- Examine the role of partners and partner training in the use of augmentative communication.
- Examine the augmentative communication needs of individuals on ventilators.
- Use current knowledge about speech perception to guide investigations of computer speech recognition as a means to computer access for individuals with severe impairment of speech and hand function.
- Compare and contrast the social acceptability of various features of augmentative communication devices including the various "voices" (e.g., male and female) employed in speech synthesis and

provisions for adjusting rate or emotion.

- Study the intelligibility of systems that provide a speech output and identify means for improving intelligibility, based on current knowledge about natural speech acoustics and influences on intelligibility.
- Develop and evaluate treatment models for augmentative and assistive devices.
- Investigate similarities and differences in the capabilities of speakers and nonspeakers in relation to communication patterns and settings.

Speech Perception and its Disorders

Communication via spoken language normally depends not only upon the ability to produce speech, but also upon the ability to perceive crucial properties of speech through the auditory, visual and other sensory modalities. Development of spoken language rests on an intimate link between the perception and production of speech sounds. Perception provides infants with the necessary information about how mature speakers of their language community produce the sounds and contrasts required to convey linguistic messages and thus helps guide the infants' own progressive attempts to produce sounds and messages that are consistent with the patterns of that language. Research on speech perception and its disorders provides an improved understanding of how the relevant perceptual processes function; how they are influenced by experience with one's native language or later-acquired languages; how these processes operate across the lifespan; and how they are impaired by disease, trauma and other sources of disturbance. An important goal for speech perception research is to deepen the knowledge base upon which the assessment and treatment of both perceptual and productive disorders of speech in children and adults rests.

The great majority of children have perceptual abilities that are at least adequate to the task of supporting normal speech and language development. However, for a substantial minority of children, diverse impairments in speech perception abilities can affect their acquisition of spoken language. Obviously, hearing impairments may have moderate to severe effects on development of intelligible spoken language, dependent on the degree and nature of the hearing difficulty (i.e., whether it involves the peripheral mechanisms for auditory perception, or involves more central functions of higher brain systems). In addition, other influences on children's ability to process the speech signal may have deleterious effects on their production and comprehension of spoken language. These include a variety of congenital and acquired disorders such as Down syndrome, autism, prenatal and perinatal diseases affecting the auditory and nonauditory systems of the brain and traumatic brain insults. Additionally, perceptual deficits may also be involved in, or affected by, the speech-language difficulties of individuals with speech disorders of unknown causes, such as phonological and articulatory disorders. And even for individuals who have no perceptual or productive impairment, the requirements of learning to communicate in a new language or dialect may be constrained in important ways by their experience with learning and using their first or native language.

Difficulties with the perception of speech, because of the limitations they may place on spoken communication and comprehension of spoken messages, can have broad negative effects on social participation, educational achievement, employment opportunities, productivity, and emotional adjustment. For example, research has indicated that deficiencies in the perception of phonetic and phonological information in speech may be associated with difficulties in reading and writing abilities, which are so critical to education and employment in an increasingly literate, technologically advanced society.

There a great need for additional research on the basic properties of speech perception and its development in normal individuals. For instance, there is a dearth of information about how fluent speech is processed; how this ability is affected by higher-order knowledge of language, such as its prosodic and syntactic organization; and how it may be affected by sources of interference such as background noise. At an even more basic level, it is still not known what sort of information infants extract from the speech they hear around them, and how they employ that information to begin to discern the words and grammatical processes of their native language. Knowledge gained from studies of these basic processes in speech perception should ultimately aid in improving early diagnosis and treatment of infants and children at risk for speech-language impairments or delays.

There is also a tremendous need for additional research on how speech perception abilities are affected by the normal aging process, as well as by the emergence of age-related disorders and breakdowns such as Alzheimer's dementia and the functional decline of multiple sensory systems. Continuing improvements in medical technology have resulted in an extension of the average lifespan, with an increasing proportion of the national population over 65 years of age. It is, therefore, increasingly important to understand the effects of aging on spoken communication and to improve our diagnosis and treatment of related difficulties with speech perception and production.

Speech perception research has clarified many issues in speech, its development and its disorders. Recent advances in computer technology, experimental methodology and theoretical modeling of speech processes have led to great improvements in our

knowledge about speech perception, as well as in our ability to further investigate perceptual abilities. Scientific insights have also been fostered by increasing collaborative efforts, particularly by cross-language and cross-cultural comparisons, and by increasingly interdisciplinary approaches to understanding the influence of biological and experiential influences on speech perception, including the fields of psychology, linguistics, computer science, engineering and neuroscience, among others.

Early Development

Native Language Development

- **Encourage studies to determine when infants begin to learn about specific aspects of native language sound patterns, its prosody including rhythmic and tonal properties, phonetic elements and phonotactic, syllabic and morphologic structure.**
- **Foster research that can provide critical information about when various general features of language structure, such as phonotactic patterns, are acquired relative to other features, such as prosodic patterns.**
- **Investigate the range of acceptable or normal individual variability in the acquisition of particular types of language-specific information.**
- **Pinpoint how the sound structure of the native language interacts with basic perceptual capacities during language acquisition.**

Development of Categories

- **Investigate the nature of the infant's representation of speech information and how it changes as a result of experience with a native language. This research will include obtaining more information about the type of representational units that are encoded in listening to speech, including the size of the unit; whether they are general prototypes or specific to individual talkers; and whether they are characterized by acoustic or articulatory properties.**
- **Examine the experiential, biologic and specific linguistic factors that might lead to modifications of representational units.**
- **Determine whether there are individual differences in the types of representational units used by infants and young children in perceiving and producing speech, the relationship between perceptual and productive units and the consequences this relationship may have for later language acquisition.**

Fluent Speech Perception

- **Delineate the basic perceptual capacities of infants and children to** discriminate fine differences in speech sounds and obtain information about how such capacities are used in processing fluent speech.

- Determine how and when infants and young children develop the ability to extract information from fluent speech and the nature of the information that is extracted.

- Obtain a better understanding of whether and how infants and young children are able to follow speech in noisy backgrounds, whether there are individual differences in their ability to do so, and how speech information helps children build a lexicon.

- Evaluate the extent to which infants and children are able to cope with the variability in speech. Investigations into the capacity of infants and children to cope with talker, dialect and rate differences in speech are important for understanding normal development and for improving early diagnosis and treatment of speech perception difficulties in young children.

Neural Foundations

- Investigate the relationship of developmental changes in speech processing to changes in the structural and functional development of the nervous system. Studies that relate changes in speech processing to neural changes may yield new insights about the mechanisms responsible for developmental changes.

- Examine the relationship between neural development and individual differences in the timing and acquisition of certain milestones associated with phonologic development.

Characteristics of the Input

- Provide empirical data that could help to settle long standing debates regarding the role of innate and experiential factors in language acquisition. Specific questions to be examined include the extent to which adults enhance phonetic contrasts or engage in phonologic reduction when they address young children.

- Measure the acoustic characteristics of speech directed to infants and the frequency with which such patterns occur. This information should be helpful in understanding the developmental process.

- Improve theoretical models of the ways in which innate and experiential factors interact during the course of language development. Such studies may be helpful in determining the extent to which the acquisition of knowledge about the native language sound system may influence other aspects of speech perception and language development.

Modeling

- Encourage attempts to model the ways in which native-language phonetic and phonologic categories develop from basic speech perception capacities. In particular, modeling approaches may aid in evaluating the extent to which the processes underlying the development of phonologic categories are specific to speech and language, or derived from more general cognitive and perceptual processes.

- Develop theoretical models that attempt to deal with the integration of prosodic and phonetic information in the perception of speech. These models should prove valuable in understanding how fluent speech processing develops.

Multimodal Factors

- Compare and contrast the perception of speech and manually coded languages by young children in both language groups.

- Identify the role that specific brain structures play in the acquisition and comprehension of language in the vocal modality versus the manual modality.

Influence of Higher-Order Knowledge

- Relate changes in speech processing to achievements in other levels of linguistic knowledge (morphology and syntax). These findings should provide insights about how sources of information interact in speech perception.

- Study the contributions to speech processing provided by information in the visual, haptic and proprioceptive modalities, as well as the deficits that occur when such sources of information are not available. This would help clarify the nature of the mechanisms underlying speech perception and provide useful information regarding its implications for persons who are hearing impaired.

- Investigate the relationship between the development of speech perception and important developmental changes in cognitive abilities. This information will have major clinical and theoretical implications.

Adulthood

Nature of the Speech Signal and its Perception

- Gain a better empirical understanding of which properties of speech perception are invariant and which are context-dependent.

This information would aid in understanding how listeners perceive speech in less than ideal conditions, in developing automatic speech recognition devices, as well as in improving augmentative and assistive devices, and in determining those cues or properties that are apt to be vulnerable to neurogenic insult.

- Examine the properties of utterances that adult speakers direct to mature learners of a second language, such as speech rate, intonation and phonetic clarification. Compare those with the properties of speech directed to native adult listeners and to young first-language learners.
- Determine the means and extent to which listeners are able to extract and remember information about talker identity, emotional tone and other nonlinguistic information from the speech signal, and how this information may interact with the processing of linguistic information.
- Investigate the auditory transformations of complex signals to determine how this process structures and ultimately shapes human speech. It is also important to identify the acoustic properties that are information sources about the articulatory gestures used to produce speech.
- Investigate the extent linguistic experience and listener characteristics, such as individual variation and special populations, affect how information is extracted from the speech signal.
- Conduct research to identify the processes listeners use to track speech in the midst of noisy environments, including competing speech signals. This information is important not only to an understanding of normal speech perception but also in identifying deficits in speech, hearing and language, and in developing automatic speech recognition devices.

Influence of Higher-Order Knowledge

- Study the nature of information the listener extracts from the prosody of utterances. This information will help clarify the representation of the input developed by the listener during on-line processing.
- Investigate the role played by factors related to the organization of the lexicon (word frequency and number of phonetically similar items), as they influence speech perception. Information from such studies may have important implications for understanding the nature of deficits in individuals with language impairments.

Modeling

- Develop models that describe how listeners extract linguistic meaning from spoken input. Such models have importance for research on natural language understanding, automatic speech recognition devices and the development of better clinical tools for identifying and treating language and hearing disorders.
- Provide complete details on competing models of speech perception so that they can be empirically tested. Empirical testing would enable investigators to converge on the correct account of speech perception mechanisms and provide a theoretical framework to pose research questions, to establish research strategies and priorities, and to develop efficacious assessment and treatment strategies.
- Model how the acoustic signal is transformed by peripheral and central auditory processing mechanisms, which will be valuable in constructing theories of speech perception.
- Encourage cross-species studies that model the way complex, biologically relevant signals are perceived.
- Develop computer simulations that attempt to model recognition of fluent speech as a useful way of evaluating the feasibility and psychological plausibility of speech processing models.

Cross-Language and Second-Language Learning

- Pinpoint differences in categorical representations of native and nonnative listeners and elucidate the extent to which categorical representations may change upon exposure to a second dialect or language.
- Test for differences in syllable processing strategies that might arise from language-specific differences in phonotactic constraints (rules that govern sound combinations) or syllable organization.
- Determine differences in degree of attention to various aspects of the speech signal that might arise from language-specific differences in phonetic and prosodic patterns.
- Extend previous psycholinguistic research that has concentrated on the role of lexical familiarity to the study of perceptual adjustments during second-language learning.
- Quantify the role of age in second-language learning or duration of use of English as a second language on English language comprehension, in both ideal and non-ideal listening conditions and with single and multiple talkers.

- Foster the development of multisite national and international research collaborations and networks that are needed for high quality cross-language and cross-dialect studies.

Fluent Speech Processing

- Investigate the processes involved in the perception of fluent speech and the sequencing and interaction of those processes in on-line perception.

Neural Foundations

- Encourage the investigation of brain mechanisms involved during on-line speech perception.
- Foster studies that will provide a broader picture of the full range of speech capacities in brain-damaged, neurogenic-impaired and other special populations, such as persons who are bilingual or congenitally deaf or blind.
- Develop a fuller understanding of the organization of the auditory pathways and central brain structures and functions that are relevant to speech processing.

Aging

- Conduct studies investigating speech perception skills in the normal elderly and in the elderly following gradual or sudden hearing loss or brain damage.
- Develop standardized assessment protocols that quantify speech perception capabilities in the elderly, based on recent experimental findings, especially for detecting perceptual difficulties in the elderly experiencing cognitive deficits (multi-infarct dementia and Alzheimer's disease) and those experiencing multisensory losses (hearing and vision).
- Determine whether changes in speech perception normally occur with aging and, if they do, assess the extent to which they affect language comprehension skills.

Disorders Affecting Speech Perception

Peripheral Auditory Disorders

- Investigate the perceptual consequences associated with conductive hearing losses.
- Conduct developmental studies of speech perception in children with varying degrees of sensorineural hearing impairment.
- Evaluate the influence of alternative sensory devices, such as tactile aids, hearing aids and cochlear implants on speech perception in hearing-impaired populations.

- Investigate the influence of different speech processing strategies on speech perception involving the use of various assistive sensory devices.
- Conduct treatment efficacy studies evaluating aural rehabilitation techniques used to improve speech perception and production in individuals with hearing impairments.
- Improve the assessment of speech perception skills in people with hearing impairments based on the study of normal speech perception.
- Encourage studies designed to assess speech perception using tasks which do not require higher-order language skills.
- Explore the perceptual consequences of auditory only, visual only and combinations of auditory-visual presentations to individuals with hearing impairments.
- Study the psychoacoustic characteristics of persons with hearing impairment and how these characteristics relate to speech perception.
- Conduct studies exploring the relationships of speech production and perception in persons who are hearing-impaired.
- Promote studies examining the wide range of performance variability in individuals who are hearing impaired to elucidate why some achieve higher performance than others on measures of speech perception and production.

Central Auditory System Disorders

- Study the speech perception and production skills of children with central auditory processing disorders.
- Examine the consequences of neurogenic disorders and insults, such as aphasia, apraxia, brain injury, Parkinson's disease, amyotrophic lateral sclerosis, on speech production and perception. Investigations of these disorders may provide particularly important insights regarding the relationship between speech production and perception and their breakdown.

Phonological Disorders

- Isolate the basic perceptual abilities of young children and identify how the abilities change with normal development. These data will provide a baseline for comparison with the perceptual skills of children who are affected by phonological disorders.
- Establish parallels between the development of perceptual categories and the emergence of the

productive phonology in children, especially with respect to identifying the basic units of phonological systems in the perception and production of speech.

- Determine the nature, degree and extent of perceptual breakdown in speakers with productive phonological disorders.
- Develop and evaluate reliable and valid methods of assessing perceptual deficits in speakers with phonological disorders.
- Determine the efficacy of the perceptually based, as opposed to production-based, treatment of phonological disorders.
- Isolate the contribution of speech perception to disorders of phonology and determine the role of perception in treatment.

General Topics

- Continue to investigate the relationship between reading proficiency and speech perception capabilities in good and poor readers. Contrast the performance of good and poor readers on tasks manipulating input modality (visual versus auditory versus multimodal) and cognitive demands (memory load) as well as linguistic factors (lexical familiarity or phonological structure).
- Explore the speech perception capabilities and limitations of individuals with autism.
- Initiate studies evaluating speech perception performance and difficulties in other populations with communication disorders (developmental language impairment) or conditions which place individuals at risk for communication disorders (substance abuse, HIV infection or lead poisoning) to assess the perceptual contributions to communication difficulties.
- Examine the relationship between cognition capabilities and speech perception in individuals with mental retardation syndromes that are nonspecific for communication deficits, such as Down syndrome or Williams syndrome.
- Investigate the effects of traumatic brain injury on speech perception and its relation to speech production and language in affected individuals.

Cross Cutting Topics

Research Methodologies

Conceptual Underpinnings

- Encourage research designs that examine the contributions and interactions among biological, experiential and social factors in all areas of speech production and perception development.

- Conduct research on speech perception and speech production within a developmental, lifespan perspective, using longitudinal as well as cross-sectional and single subject designs, and retrospective as well as prospective approaches.

- Base speech perception and production research on clear tests of hypotheses derived from theoretical models that generate testable hypotheses.

- Encourage increased application of molecular genetic and biologic techniques to the study of speech and speech disorders.

- Conduct genetic research on speech disorders, including description of behavioral phenotypes and family linkage.

Measurement Issues

- Develop standardized acoustic, aerodynamic and kinematic measurements of speech production.

- Develop culturally sensitive assessment instruments for studying multilingual and multidialectal and nonnative language populations.

- Develop protocols based on current scientific knowledge of normal populations and that include recognized clinical criteria for disorders and for relevant subclinical or variant conditions.

- Develop new methods and tools for studying on-line perception of fluent speech and for studying the range of variability in speech production and perception.

- Encourage the development, refinement and use of new and emerging technologies in speech research and clinical applications. These include, but are not limited to, brain imaging techniques, genetic studies, neurochemical approaches, measures of speech articulatory events, computer modeling and simulations, automatic speech recognition and synthesis.

- Develop techniques for collecting reliable and valid data on the perception and production capacities of the toddler, preschooler and the young school-aged child.

Research Approaches and Designs

Descriptive Studies

- Determine the incidence, prevalence and occurrence of disorders of speech perception and production, including potential racial, ethnic and gender differences.

- Examine the range of normal variability in speech perception and production, including multicultural and gender differences.
- Characterize the relationship between speech disorders and broader sociocultural factors that may be affected by the disorders, such as academic performance, school drop-out rates, employability, continuing education and training in changing job markets.

Analytic Epidemiology

- Conduct case-control (retrospective) and cohort (prospective) studies to: identify risk and protective factors (including genetic factors) for disorders of speech perception and production, quantify risk and examine concurrent conditions. Studies may include individuals with anomalies and investigations of early indicators.
- Apply current techniques of molecular genetics and familial linkage research to elucidate the hereditary basis of various disorders of speech production and perception. Special concern should be paid to bioethical considerations in this and other approaches characterizing biological markers and risk factors in speech disorders.

Experimental Research Strategies

- Establish a program of developmentally appropriate, controlled clinical trial research.
- Extend treatment studies to include follow-up evaluations on retention, comparisons of long-term versus intermittent treatment, incidence of relapse and age of intervention.

Other Research Designs

- Support longitudinal studies as a means of providing in-depth developmental data on normal and disordered development.
- Encourage and support studies comparing various factors in differing communities and cultures in order to describe variations in communication behaviors in various ethnic and racial groups.

Multicultural Issues

Normative Data

- Develop communication ability norms in the areas of speech perception and speech production. Available normative data should reflect the cultural and linguistic diversity of the United States population.
- Develop cross-cultural and cross-ethnic investigations of acoustic

parameters of speech. Also include studies of the anatomic and physiologic bases of diversity in speech production and speech perception across subgroups of the multicultural population.

Incidence, Prevalence, Risk Factors and Utilization of Rehabilitation Services

- Conduct epidemiologic surveys to determine the incidence and prevalence of communication disorders (including auditory disorders and disorders resulting from laryngeal cancer, cleft lip and cleft palate) for populations from the multicultural community.
- Conduct epidemiologic studies to uncover the effects of important independent variables such as, poverty and race, on the incidence and prevalence of various communication disorders.
- Delineate the specific health and environmental risk factors associated with various categories of communication impairment among people from different multicultural communities.
- Conduct rehabilitation needs assessments for populations from the multicultural community.
- Determine the factors that influence access to and utilization of rehabilitation services for populations from the multicultural community.

Research Topics Unique to the Area of Multiculturalism

- Determine the effects of sickle cell disease and other disorders associated with specific populations on the communication process.
- Investigate the influence of culture and cognitive style on treatment effectiveness and efficacy.
- Investigate treatment efficacy and clinical practices that are implemented with bilingual and bidialectal populations.
- Investigate second language or second dialect development in multilingual and multidialectal speakers.
- Investigate the influence of second language and dialect learning on the development of various aspects of normal speech and communication, such as fluency.
- Investigate the influence of multilingualism and multidialectalism on the development of speech in children with communication disorders.

- Investigate the influence of multilingualism and multidialectalism on treatment for speech impairments in adult populations.
- Conduct cross-cultural research to determine specific cultural perceptions regarding factors that constitute impaired speech production and impaired speech perception.
- Develop culturally and linguistically appropriate assessment procedures to facilitate the identification of language impairment (versus language difference) among individuals from culturally and linguistically diverse populations.
- Develop culturally and linguistically appropriate treatment paradigms and models of service delivery for individuals from the multicultural population.
- Develop procedures for determining the most effective language of treatment for multilingual and multidialectal speakers.
- Investigate the social implications of nonstandard English language and dialect as a function of the educational, vocational and social contextual setting and listener variables.

Language and Language Impairments

Language is the uniquely human means of communication through which knowledge, belief and behavior can be explained and shared. The broad goal of research on language is to understand the nature of normal language function, including the underlying bases and mechanisms involved. A primary purpose of this work is to build the foundation necessary to develop and evaluate intervention strategies designed to improve and enhance communication for individuals with language disorders. The understanding of normal language (whether spoken, signed, or written) provides a basis for comparison in investigations of language disorders. It is critical to understand how language is produced and understood, what its biological and neural substrates and organizing principles are, how it is learned by children and how it is processed in adulthood.

Language acquisition takes place naturally for most children, including those who have normal hearing and those who are deaf with signing deaf parents. However, much research is still needed before normal language acquisition can be fully understood. There is an especially great need for data from all of the diverse groups of children that make up contemporary U.S. society. In light of the growing role played in society by different racial, ethnic and social groups, it is essential that these populations be properly represented in the subject pools for studies of normal language processes.

Individuals with normal hearing, as well as those with hearing impairment, may exhibit a disorder of language, that is, problems with language comprehension, production or use sufficient to interfere with interpersonal communication. In young children, these disorders frequently involve difficulty in the acquisition of the ambient spoken or signed language and may also lead to impairment in reading and writing. In adults and older children, persons with language impairment include aphasic individuals who have lost their previous levels of language competence as a result of brain injury.

Disorders of language affect children and adults differently and pose different sorts of research questions. For the child who does not use language normally from birth or who develops the impairment in childhood, the disorder occurs in the context of a language system that is not fully developed. In contrast, impairment of language in adults disrupts a system that may be less malleable in the face of neural damage. As a result, although the broad goals of research on language disorders are similar whether the affected individuals are children or adults, the research agendas for these two groups are considered separately.

Both the review of research accomplishments and the discussion of research opportunities are divided into four general areas. The first of these concerns multicultural issues. This area receives emphasis because, with U.S. society becoming increasingly diverse, it is vital that evaluation of language ability be based on representative normative data. Moreover, there are indications that particular disorders may be more prevalent among certain groups; the development of preventive measures must rely on a clear understanding of the distribution of, and underlying bases for, language disorders in the population at large.

A second general area concerns language among deaf children and adults. Although much has been learned about the natural acquisition of signed languages, many details of the nature of this process are still unknown. Furthermore, many deaf children who acquire a signed language with little difficulty nevertheless have significant problems learning to read and write. Another important consideration is the fact that large numbers of individuals, including those whose hearing impairment was acquired during childhood, use spoken language as their primary mode of communication. The language acquisition and use of many of these people are characterized by difficulties not faced by most hearing persons.

A third general area deals with language disorders in children. These disorders can be discussed in terms of whether the language difficulties exist in isolation or in association with other problems and whether the factors interfering with language were present from birth or appeared later. Many children with isolated language problems present from birth are given the clinical label of "specifically language impaired." Children with language disorders occurring in conjunction with other developmental disorders include children with mental retardation and those with autism, among others. Finally, a number of children begin the language learning process normally but then acquire a language disorder through infection, stroke or trauma.

The topic of language disorders in adults constitutes the fourth general area of concentration. The primary cause of such disorders is a focal brain lesion, caused by a stroke or head injury. Language disorders can also occur as a primary symptom of progressive dementing illnesses. In both cases, the previously-normal language system is changed in ways that can be devastating to the economic and social well-being of the affected individuals. Recent research on adult language disorders has emphasized the wide range and combination of language symptoms that can occur when the brain is damaged. This diversity of language impairments complicates efforts to understand the underlying functional bases for these disorders, to link particular symptoms to specific brain regions and to design effective rehabilitation techniques.

For all four of these areas of focus, current research opportunities emphasize studies that enhance understanding of the normal language system, while clarifying the various ways that language or language acquisition can break down. In all areas, successful intervention to address language impairments must be based on precise knowledge of the ways in which the disordered condition differs from the normal case.

Major Scientific Opportunities

Multicultural Issues

Specific research relating to multicultural issues should:

- Include normative studies for different languages or social dialects which focus on the acquisition and use of phonological and grammatical forms as well as content and pragmatics. Investigations of the simultaneous or consecutive acquisition of two or more linguistic systems are also necessary. Such research can include investigations of "critical periods" for dual language learning and code switching.
- Obtain basic epidemiologic information on the incidence and prevalence of and risk factors for speech, language and hearing disorders within African-American, Hispanic, Asian/Pacific Islander

and Native American populations, as available data may not be generalizable across these groups.

- Explore factors that might impede the efficacy of treatment, such as differences in cognitive or learning styles and cultural systems of belief.
- Develop means of differentiating between language differences and disorders across cultural groups.
- Investigate the incidence and prevalence of and risk factors for adult neurogenic impairment among culturally diverse and bilingual populations

Language and Deaf People

Language Development in Deaf Children

Within this area, new studies are needed to:

- Identify and describe patterns of acquisition of American Sign Language (ASL), particularly when access to a first natural language is delayed or incomplete.
- Identify and describe patterns of language acquisition of children exposed primarily to systems or styles of signing in which the intention is to model or support English speech.
- Identify and describe patterns of language acquisition among children exposed primarily to oral language.
- Identify and describe patterns of language acquisition of children primarily exposed to spoken English through Cued Speech.
- Identify and describe patterns of related cognitive, psychological and academic deficits accompanying delayed language acquisition.
- Study the nature and value of language models provided by hearing adults in contact with deaf children. This research should include studies of the nature of receptive and productive aspects of English-like signing in addition to aspects of auditory, oral language models.
- Identify deaf children who have language disorders by examining and describing the differences between normal and language-impaired deaf children.
- Study approaches and techniques for the training of hearing parents of deaf children to sign or to facilitate the development of their children's spoken language, including the use of Cued Speech.
- Identify and describe the processes of reorganization of the input language, particularly

pidginization and creolization processes in language contact situations.

- Identify and describe the invention of gestural language systems without formal sign input and the relation of this process to eventual signed or spoken language development.
- Study approaches and techniques for evaluating the potential of new technology and intervention strategies (such as auditory prostheses, laser disk technology, computer-based training systems) for promoting spoken language acquisition by deaf children.
- Identify critical periods for both the natural acquisition and training of spoken or signed language by deaf children.
- Develop the means of identifying language disorders in deaf children from different cultures.

Studies of Literacy in Deaf Children and Adults

Research should be conducted to:

- Study the nature of processing text by successful deaf readers in an attempt to identify the most effective strategies, both auditory and visual, for the teaching of literacy to deaf people.
- Develop and test new strategies and techniques for teaching English as a second language to deaf children who make use of their capabilities for visual language processing.
- Study the role of captioning, telecommunication devices, personal computers and other technological influences on the improvement of deaf children's literacy skills.
- Study the relationships between speech processing and literacy in deaf children who use spoken language primarily.
- Study the relationships among speech processing, sign processing and literacy in deaf children who use sign language.
- Develop and evaluate appropriate and psychometrically-sound tests of psychosocial, intellectual and academic development and of first- and second-language acquisition by deaf children and adults under a variety of language use conditions.
- Examine the interaction of acquisition of signed languages with spoken and written language and begin to characterize the resulting bilingualism. Studies of the order of acquisition of speech and signed language as they affect children's eventual acquisition of English language and literacy should also be conducted.

Basic Research on Sign Language Structure and Function

Investigators should be encouraged to:

- Continue research on brain mapping for sign language functions.
- Develop improved techniques for imaging sign language motions in three-dimensional space.
- Conduct further investigations into how deaf people perceive and process visually. Studies could include investigations of the relation between limb control and vision and of the functioning of deaf people with visual disorders.
- Conduct studies of the nature of parallel processing of language, such as the simultaneous processing of visual and auditory information.
- Expand studies of the brain and language, such as those on the specialization of the cerebral hemispheres for language and other cognitive processing.
- Study signed language and other languages used by the deaf community from functional/psychological and structural/linguistic perspectives. Studies should focus on the nature of the "creolization" of signed language and the effect of interaction of modality and language structure, including contact signing.
- Study signed languages other than ASL and varieties of signing within ASL, to identify the role of cultural and ethnic differences on signed language use by deaf people.
- Study other signed languages, such as simultaneous communication and signed English, relative to the acquisition of English language by deaf children.
- Relate infants' early acquisition of sign language phonology, assessed through tests of sign perception, to the acquisition of the higher levels of language, such as the acquisition of words (lexicon), word meanings (semantics) and grammar (syntax).
- Investigate basic and higher level processes underlying vision, including the requirements of structured use of space and movement, the processing of complex dynamic arrays and the perception of motion and form.
- Study the impairments to sign perception in deaf individuals who become aphasic or who sustain other cognitive impairments subsequent to brain damage.

Language and Its Disorders in Children

Bases of Language Disorders in Children

Research should be carried out to:

- **Examine the linguistic profiles of language-impaired children to determine if they vary according to the type of language being acquired (e.g., morphologically rich vs. sparse; flexible vs. rigid word order). The weaknesses observed in language-impaired children across these languages might reveal a common factor that may be the source of the disorder.**
- **Examine the impact on language production of structural anomalies of the speech mechanism, such as craniofacial anomalies, long-standing tracheotomies or severe neuromotor impairment. The relative contribution of subtle motor speech problems to certain subtypes of language impairment is not known.**
- **Study the normally developing brain across the lifespan using a wide range of anatomic, physiologic and metabolic techniques. New advances in imaging the brain (anatomic, physiologic and metabolic) are particularly important to apply to studies investigating normal and abnormal development.**
- **Conduct multidisciplinary studies that combine imaging techniques with fine-grained behavioral analysis of processes underlying language development and disorders.**
- **Determine the reason for the much higher prevalence of developmental language disorders in boys than girls.**
- **Isolate those cognitive areas not represented in IQ tests and determine whether or not these areas interact with language functioning.**
- **Determine to what extent language impairment may be secondary to psychosocial disorders.**
- **Determine to what extent psychosocial disorders may result from a primary language impairment. There are special groups of children and youths who are at risk for language disorders and language-based learning disorders. These special groups include victims of abuse, neglect or drug- or alcohol-related lifestyles and homelessness and general victims of poverty.**
- **Determine to what extent failures in communication and education are related to psychosocial factors.**

Assessment

Initiatives are needed to:

- Develop psychometrically sound and culturally fair and sensitive procedures for the measurement of language comprehension and production to be used in identifying and classifying language impairments.
- Develop alternative assessment strategies including criterion-referenced testing, observational techniques, interview procedures and other informal strategies.
- Explore the utility of state-of-the-art computer technology in language assessment including language sampling analysis.
- Develop assessment strategies which have application, validity and reliability for identifying language disorders in children in a variety of assessment contexts (e.g., school, home, clinic).
- Determine the most appropriate strategies for evaluating limited-English-proficient (LEP) children including the use of interpreters or informants.
- Develop assessment tools for preschool populations, especially for children under three years of age.

Academic, Social and Vocational Impact

Research is needed to:

- Study the relationship between language disorders and subsequent or concomitant learning disabilities.
- Study the relationship in children between language disorders and social adjustment problems.

Intervention

Research must be conducted to:

- Develop new intervention strategies based upon current theoretical models and establish their efficacy.
- Determine the efficacy of currently available intervention strategies through both single subject studies and studies of children who clearly represent different types of language impairment.
- Evaluate alternative models of service delivery such as family- or school-based programs versus direct delivery by speech-language pathologists.
- Investigate the use of computers and recent technologic advances (for example, in speech recognition and speech production) in

intervention with language-impaired children and with deaf children learning oral language.

Language and Its Disorders in Adults

Brain-Language Relations

Detailed study is needed to:

- Investigate the mechanisms by which recovery takes place and the basis for individual differences in recovery, using a variety of techniques for indexing brain activity in vivo (e.g., positron emission tomography, single photon emission computed tomography, event-related potentials).
- Clarify the role of the non-dominant (typically right) cerebral hemisphere in the assumption of language functions following damage to the dominant hemisphere.
- Relate specific symptoms to discrete brain regions using lesion analysis. A correlation between the breakdown of motor speech planning and structural brain lesions has been demonstrated, but other potentially localizable language skills (such as speech sound discrimination and oral word comprehension) are still inadequately mapped.
- Define by clinico-anatomic study the link between processes that are closely related to well-localized structures and those that are broadly distributed in the language zone.
- Identify well-defined forms of selective impairments through detailed study of individual cases, including careful analysis of brain lesions and of functional language impairment.
- Explore the role of various neurotransmitter systems in the mediation of particular language operations. The potential for pharmacological treatment follows directly from such understanding.

Analysis of Processes Underlying Language Disorders

Continued study is needed to:

- Extend recent progress in the cognitive sciences to an understanding of the structure of normal language processing. For example, techniques involving real-time analysis of normal-language processes should be adapted to examine the nature of language pathology.
- Distinguish the various forms of dysfunction that characterize oral/aural, written and signed languages through comparative study of impairments in those modalities.

- Elucidate the relationship between deficits that are specific to the language system and those that arise from perceptual, motor, or other cognitive disorders and clarify their relative contributions to complex language impairments. Information about such relationships could provide an important basis for the design of new treatments.

- Continue comparative analyses of disorders in different languages, on the assumption that language-specific differences in symptoms can help reveal the linguistic and cognitive mechanisms that subserve language processing.

- Develop artificial intelligence computer models that simulate normal language and its disorders.

Assessment, Intervention and Recovery

Specific opportunities in these areas include efforts to:

- Demonstrate the efficacy and efficiency of the existing intervention strategies for aphasia treatment. Such demonstrations will require development of new approaches to the evaluation of efficacy which use both single subject and group methods.

- Revise and improve existing assessment procedures in order to bring them into line with current understanding of the relationship of patients' symptoms to causal underlying language deficits.

- Develop a workable diagnostic scheme that provides a rational basis for the classification of patients and for comprehensive characterization of their deficits.

- Develop functional assessment tools to evaluate the communicative abilities of language-impaired individuals.

- Study the patterns of symptoms in patients with disorders in which deterioration instead of improvement is the natural course, for example, in Alzheimer's disease. Identification of predictors of the course of progression of language disorders in such patients would contribute to their management and provide a basis for approaching intervention.

- Develop and evaluate computer-assisted instruction as an intervention strategy for working with aphasic individuals. In particular, strategies that capitalize on recent information concerning the functional basis of specific language symptoms or that provide aphasic individuals with workable compensatory mechanisms should be developed.

- Develop and evaluate alternative and augmentative communication systems for adults with language deficits. Adults severely impaired in understanding and producing language may be capable of effective communication by alternative means, including computer-based systems.

- Investigate social and cultural factors that have the potential to affect treatment outcome and evaluate the relative contribution of these factors to individual differences in response to treatment.

Comparative Language Studies

New initiatives are needed to:

- Obtain normative data from healthy individuals of various ages to determine whether or not there are changes throughout the lifespan in the use of spoken, written or signed language.

- Develop normative data on adults from a range of social strata and linguistic and cultural backgrounds to provide a basis for addressing the contributions of sociocultural factors, bilingualism and normal aging to language impairments.

- Compare analysis of left- and right-brain damaged hearing subjects to determine the extent to which the right hemisphere may be involved in language use. Study brain-damaged users of sign language in order to understand hemispheric specialization for complex linguistic properties conveyed through spatial mechanisms.

- Study the differences that exist between the language disorders of focally brain-damaged patients and those that accompany more generalized brain dysfunction. Comparisons among the forms that language breakdown can take secondary to these various causes have suggested important functional dissociations, but further study is required to clarify the nature of and underlying bases for these differences.

- Develop normative data on the language functioning of diverse populations to provide a substantive basis for approaching their language disorders. The population of the United States is increasingly multilingual; as this population ages and its risk of stroke and consequent aphasia increases, there will be an increasing number of bilingual individuals with language disorders.

HEARING AND HEARING IMPAIRMENT

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HEARING AND HEARING IMPAIRMENT

Overview

Prevalence, Incidence and Cost of Hearing Impairment

More than 28 million Americans are believed to have impaired hearing. Levels of hearing impairment vary from a mild but important loss of sensitivity to a total loss of hearing. Approximately one of every 1000 infants is born with a hearing impairment that is severe enough to prevent the spontaneous development of spoken language. Many more infants have a less severe but substantial impairment or will acquire one by age three or four. Over 50 percent of these impairments are believed to be of genetic origin. These impairments have serious and far-reaching implications for all aspects of development, and the costs of treatment and education for these children are enormous.

The most common cause of hearing loss in children is otitis media, an infection in the middle ear. Otitis media is predominantly a disease of infants and young children. Recent studies show that about 75 percent of all American children have an episode of otitis media by the time they are three years of age. This disease is estimated to account for over 10 million visits to the offices of physicians per year and to have a total annual cost of over $3.5 billion. The cost of managing otitis media is enormous, but it pales in comparison to the developmental and educational sequelae of otitis media.

The number of hearing-impaired people in the United States is expected to increase substantially in the next few decades due to increasing longevity and the consequent overall aging of the population. By far, the largest group of Americans suffering from hearing loss are the elderly. Thirty to 35 percent of the United States population between the ages 65 to 75 years have a hearing loss severe enough to require a hearing aid. The percentage increases with age, and 40 percent over the age of 75 years would benefit from amplification with a hearing aid. The costs of managing hearing impairments in the elderly are enormous and growing, but they are overshadowed by the costs in terms of quality of life. There are many and obvious benefits of eliminating or alleviating hearing impairments in the elderly. Recent advances in drug therapy suggest that it may be possible to replace neurotransmitters of the auditory system that are diminished in the aging process.

Hearing impairment includes auditory disorders that are not necessarily accompanied by a loss of sensitivity. Auditory processing disorders occur in learning disabled children.

A substantial number of hearing impairments are caused by exposure to noise, either in the workplace or as a result of leisure activities. Strategies need to be developed to educate the public on the importance of preventing noise-induced hearing impairment. The costs associated with prevention are minimal compared to the enormous costs of rehabilitating individuals once affected.

At least 15 percent of the population are affected by tinnitus, many so severely that it disrupts their lives. The socioeconomic impact of this form of hearing disorder is great but has not been fully quantified.

Historical Background

Research on hearing impairment has not progressed as well as on other disorders. Research on the ear and the processes associated with hearing and its disorders was inhibited for many years by the fact that the tiny sensory organ for hearing, the organ of Corti, is encased by the bony cochlea (shaped like a snail shell) and was inaccessible to direct observation and experimental manipulation. The cochlea was, in fact, a "black box," which could be investigated in the living state only by indirect methods. Studies of pathology were also difficult, since the preservation and histologic preparation of the delicate structures of the inner ear were complicated by the presence of the surrounding bone.

There is insufficient public appreciation of the vital importance of good hearing to overall health and employment opportunities. All societies depend upon the mutual abilities of their citizens to understand and produce speech and language. Hearing is essential to everyday human communication, and yet it is taken for granted much more than other areas of health. Furthermore, hearing is widely and thoughtlessly abused.

Some individuals who do not hear are members of a cultural community with its own language, American Sign Language. There is great interest about the nature and acquisition of signed language and about visual processing of language by deaf people within the 1991 update of the Language and Language Impairments section of the National Strategic Research Plan.

Recent research on deafness and hearing impairment has benefited greatly from major advances in biomedical research as a whole, such as molecular biology. Rapid advances in the molecular genetics of hereditary hearing impairment are at hand.

Hearing

Transduction and Homeostasis

The sensory cells of the auditory system are located in the organ of Corti (hearing organ) and are in contact with the fibers of the auditory nerve. The sensory cells in the organ of Corti consist of inner and outer hair cells. In the auditory system, transduction is the process in which acoustic energy is converted to electrical energy, resulting in the propagation of nerve impulses in the auditory nerve. Homeostasis is the process of maintaining a tendency of stability in the internal environment. Cochlear homeostasis is essential for the maintenance of normal hearing. Intracellular recordings from inner and outer hair cells have revealed important functional differences between the two hair cell populations. Sound energy is transduced by inner hair cells, which are now understood as mechanoreceptors. The transduction is mediated by ion channels that are directly gated by mechanical force. The hair cell's transduction channels thus differ importantly from previously characterized channels responsive to membrane potential or ligand binding.

The inner ear not only receives but also produces acoustic energy. The signals resulting from this energy are called otoacoustic emissions which can be detected with sensitive microphones in the external auditory canal. This finding has opened a new era of investigation. The source of the otoacoustic emissions is thought to be the outer hair cells. The isolation and maintenance of outer hair cells in vitro has led to the discovery that outer hair cells move in response to acoustical and electrical stimulation and changes in their chemical environment. Furthermore, the outer hair cell motility is influenced by nerves from the central nervous system to the inner ear. It is believed that the motility of the outer hair cells results in mechanical changes in the organ of Corti which make the inner hair cells more sensitive and capable of detecting fine frequency differences.

The origin of the unique fluid environment within the cochlea and details of intracochlear blood flow have been established, and the understanding of the biochemical mechanisms involved in transmembrane signaling is increasing.

Sound Processing in the Brain

When presented with the complex sounds of speech, the normally hearing listener is able to extract many different features of speech such as its frequencies, intensities, rhythm, location and identity of the speaker and the meaning of the words. The brain extracts these stimulus features by processing patterns of neural activity along different pathways to different subregions of the brain. Each pathway may be specialized to analyze only certain aspects of the sound. These parallel pathways are constructed from a complex network of nerve cells interconnected by excitatory and inhibitory synapses.

At present, our understanding of the neuronal processes underlying sound analysis is incomplete. Nevertheless, important progress has been made in some areas, such as understanding how sources of sounds are located in space and how speech and other complex sounds are coded at lower levels of the auditory central nervous system.

To understand how complex sounds such as speech are processed, a variety of anatomic and physiologic techniques are being used to measure and analyze responses to sounds from neurons located in different subregions of the brain. Neuronal activity patterns are associated with different cell types within each region and with the chemicals (transmitters) they use for interneuronal communication.

The aim is to describe, for each subsystem, the chain of neurons involved in the analysis and how the relevant information is represented in patterns of neural activity. Knowledge of the subsystems' transmitters can be critical in selectively stimulating or blocking elements of the neural circuits and thereby dissecting their functional roles or treating their disorders. This knowledge also can be used in mapping the location of different cell types by the application of immunologic or molecular probes.

In view of the complexity of the inner ear and the brain, small disturbances in normal function can produce substantial hearing impairments. To provide successful treatment strategies for hearing disorders or to design neural prostheses and therapeutic agents, there must be an understanding of the normal anatomy, physiology and biochemistry of the auditory system. Progress already made in these areas is being applied to the periphery in the design of cochlear prostheses and hearing aids and has led to great improvements in the ability to overcome the disabling consequences of many types of hearing impairments. Identification of transmitters could ultimately lead to the development of drug therapies for a variety of auditory system disorders including hearing impairment and tinnitus.

Auditory Perception

The study of auditory perception is concerned with how sound patterns are converted by the auditory system to experiences by the listener. Auditory perceptual research extends and relates work on physiologic aspects of sound coding to the resulting experience of sound.

Research on auditory perception also determines the relation between physical properties of complex sounds (such as environmental sounds and speech) and the experiences arising from them. Work on determining how listeners recognize the source of sounds or individual speakers and how they separate and locate inputs from several different sound sources is in progress. The benefits to be derived from increasing our understanding of how normal and impaired auditory systems mediate the perception of sound are many, and they include: (1) innovative designs for auditory prostheses, (2) greatly improved behavioral tests for diagnosis of specific auditory disorders and (3) improved methods for training and rehabilitation of hearing-impaired individuals.

Regeneration of Sensory Cells

Sensory cells in the ear of cold-blooded animals can be regenerated. Even in species such as birds, in which the production of sensory cells normally ceases in early embryonic development, regeneration can occur in young and adult birds. Furthermore, the regeneration of sensory cells has been shown to contribute to recovery of hearing. Recent investigations have shown that the regenerated hair cells originate from cells produced by the proliferation of supporting cells that survive at sites of damage in the inner ear. Efforts are now under way to identify the molecular events that stimulate the proliferation of those cells, so that those events or their analogs may be tested for their potential to induce sensory cell regeneration in mammalian ears where it does not appear to occur spontaneously. Investigations of sensory cell regeneration must utilize a combination of conventional methods and methods that originate from the cutting edge of biotechnology. The questions are formidable, but the potential payoff from this research may be the long-hoped for regeneration of auditory hair cells in humans.

Hearing Impairment

Hereditary Hearing Impairment

Hereditary hearing impairment accounts for at least 50 percent of congenital deafness. Syndromes in which there is some other finding associated with the hearing impairment account for 30 percent while nonsyndromic forms (hearing impairment alone) account for 70 percent of congenital hereditary hearing impairment. Of the nonsyndromic forms, 70 to 85 percent are transmitted as autosomal recessive, 12 to 27 percent are autosomal dominant and approximately three percent are sex-linked. A large percentage of hearing impairment with onset in childhood and adulthood also has a genetic basis, and an underlying genetic susceptibility probably contributes to many forms of hearing loss attributed to environmental factors such as noise-induced hearing loss and presbycusis.

The mapping of genes involved in hearing impairment will continue to provide important information and depends on the identification of families with the gene and their participation in molecular genetic studies. Location of the gene in a specific chromosomal region provides more precise information for genetic counseling and is an important first step towards isolating the gene, determining its protein product and understanding the cause of the hearing impairment.

Advances in comparative mapping of the human and mouse genomes promise to be valuable for identifying human genes responsible for hearing impairment. The insertion of genetic material into cells to prevent or ameliorate hereditary hearing impairment may soon become a possible treatment option.

Acquired Sensorineural Hearing Loss

There are a great variety of causes of acquired sensorineural hearing loss. These include: noise exposure, infections, neoplasms, trauma, degeneration and aging and immune-mediated disorders as well as unknown causes. Although the term "acquired" sensorineural hearing loss implies a nongenetic cause, there may be a genetic predisposition for the development of hearing loss from these causes.

It has been estimated that as many as 38,250 new cases of Meniere's disease are diagnosed each year in the United States. This condition results in hearing impairment and balance disturbances that wax and wane, yet continue in a progressive fashion. Despite the vexing nature of this illness, studies have led to a better understanding of the fluid homeostasis within the inner ear and the anatomical sites responsible for its maintenance. Studies of temporal bone pathology have suggested possible viral, immunologic, allergic, hormonal and environmental causes for this disease. While animal models have been developed which show some of the histologic features seen in the human condition, no model has been found which simulates recurrent attacks described in this patient population. A number of longitudinal, controlled studies on the medical and surgical treatment for this condition have been reported, however, no treatment has been shown to improve or stabilize the hearing in these patients. Furthermore, there is a disturbing tendency for this disease to become bilateral (20 to 40 percent). Therefore, there is a critical need to discover the cause of this condition and to develop treatment strategies to prevent the late sequelae of this relentless illness.

Bacterial, fungal or viral infections including acquired immunodeficiency syndrome (AIDS) can cause sensorineural hearing loss. Bacterial and viral infections may cause sensorineural hearing loss by spreading from the middle ear or mastoid cavity into the inner ear or may spread into the inner ear from the subarachnoid space as in meningitis.

Viruses have also been implicated in sudden deafness. Patients with AIDS may have hearing loss from the AIDS virus itself or from other pathogens, including viral and fungal agents that cause opportunistic infections.

The immune system is not only an important factor in the defense of the ear against infections, but it also may be involved in hearing loss in autoimmune diseases and other types of immune-mediated hearing loss. These include systemic diseases such as polyarteritis nodosa, Cogan's syndrome and lupus erythematosus, in which the inner ear may become the target organ of antibodies or become damaged by the resultant inflammatory process. Research is needed in the diagnosis and the treatment of these disorders. Special opportunities exist to study these problems because of new technology derived from molecular biology and immunology. The role that allergic processes play in the cause of hearing impairment has been suggested but requires further study to establish its relationship.

A variety of tumors may result in a sensorineural hearing loss. One of the most frequent tumors is acoustic neurinoma (vestibular Schwannoma), the most common tumor in the posterior cranial fossa. Both benign tumors and malignant tumors, such as squamous cell carcinoma and chemodectomas, may affect the temporal bone. Further studies of the natural history, genetics, factors controlling growth and treatment, including chemotherapy, radiation therapy and surgery, are needed. For example, the recent application of the gamma knife and laser surgery to the removal of acoustic neurinomas should be studied to evaluate the efficacy of these new therapeutic approaches.

During the last decade, important progress has been made in understanding how hearing loss may be caused by environmental factors such as noise, drugs and toxins. For the first time, rational hypotheses have been advanced for the mechanisms underlying hearing loss induced by aminoglycoside antibiotics, leading the way to the design of protective measures and drug modification. The understanding of inner-ear damage by diuretics has allowed the development of preventive pharmacologic strategies to be successful in animal models.

The mechanisms by which intense noise affects the inner ear are better understood. Advances include novel and important information about the effects of noise on the cochlear microcirculation, fluid homeostasis and mechanical properties of the sensory cells. These advances provide an excellent basis for future research to elucidate the molecular mechanisms underlying environmentally induced hearing deficits and strengthen the hope of finding means to prevent or ameliorate these forms of hearing impairment.

Inner ear, auditory nerve and brain stem degeneration probably contribute to the hearing disorders seen in aging persons. In most cases, no discrete cause can be found. In these instances, the term presbycusis is used. Noise exposure, both occupational and nonoccupational, is often partially responsible for the inner-ear damage observed. Some people are genetically predisposed to premature loss of hearing. Systemic illnesses such as atherosclerosis and diabetes are poorly assessed as risk factors for hearing loss in aging.

The prevalence of presbycusis has been reasonably well documented, but future population-based studies are needed to identify more clearly risk factors, including moderate (especially nonoccupational) noise exposure, smoking, diet and systemic disease. These studies should go beyond pure-tone audiometry to include measures of speech perception performance and other high-level auditory processes. Family studies can help elucidate the genetic component. Finally, epidemiologic studies should explore the impact of presbycusis on affected persons and on society.

Unfortunately, there are many disorders of the inner ear for which the cause is unknown. These include disorders as perilymphatic fistula, noises in the ear or head (tinnitus) and Meniere's disease. There is a critical need to elucidate the pathogenesis and develop treatments for these puzzling disorders.

Otitis Media, Otosclerosis and Other Middle-Ear Disorders

Otitis Media

Otitis media is the most common treatable disease of infants and young children and the most frequent cause of fluctuating hearing loss. Three-fourths of the children born each year experience at least one episode of otitis media by their third birthday, and one-third have repeated bouts of otitis media. The disease necessitates frequent health care visits for the child and parents, with an enormous impact on family lifestyle and parent work productivity. The economic impact of this disorder for families with young children is extraordinary; estimated annual health care costs for otitis media in the United States are $3.5 billion. Furthermore, some of the children who experience frequent otitis media during early childhood experience difficulty in speech and language development and some have lifelong hearing impairment. These sequelae compound the economic and societal costs of otitis media.

Remarkable advances have occurred in improving the understanding of the epidemiology, natural history and pathophysiology of otitis media. This progress is being translated into improved methods of prevention, diagnosis and treatment. New techniques of molecular and cellular biology and genetics are being applied to elucidate underlying mechanisms that predispose children to the entire spectrum of middle-ear inflammatory disorders grouped within otitis media.

Otosclerosis and Other Middle-Ear Disorders

Otosclerosis is one of the most common causes of progressive, adult-onset hearing loss, affecting one in 100 persons. It is a localized disorder of bone remodeling within the middle and inner ears. Recent advances in genetics, molecular biology and ultrastructure have improved the understanding of this disease, however, its exact cause is still unknown.

Middle-ear structures collect environmental sound and transmit it to the inner ear. An understanding of middle-ear micromechanics is essential to the development of improved middle-ear implants and implantable hearing aids.

Assessment, Diagnosis, Treatment and Rehabilitation

The identification and assessment of hearing impairment and the diagnosis of specific disorders involve collaboration among primary care physicians, otolaryngologists, audiologists and geneticists. The procedures in current use include measurement of auditory thresholds, determination of the acoustic properties of the external and middle ears, measurement of speech recognition thresholds, quantification of the acoustic reflex threshold, measurements of otoacoustic emissions and recording of the electrical activity of the brain in response to sound. Assessment and diagnosis are precursors to treatment and essential to the determination of treatment efficacy.

During the past decades, major progress has been made in the medical and surgical treatment of some hearing impairments. For the hearing impairments that cannot be alleviated by medical or surgical treatment, there is a rich array of rehabilitative intervention. This intervention has two basic components: prosthetic management and auditory rehabilitation. Prosthetic management seeks to provide access to sound patterns by means of hearing aids, cochlear implants, tactile aids, visual speech training aids and other sensory aids. Auditory rehabilitation involves training to accelerate adaptation to novel sensory inputs; develop auditory (and nonauditory) perceptual skills; enhance the integration of inputs from different modalities, such as vision and hearing; and create an emotional state that is optimally conducive for communicating. For children with hearing impairment of sufficient severity to prevent or impair the spontaneous development of spoken language, intervention and management go well beyond prosthetics and auditory rehabilitation. The development of the basic cognitive and language skills on which subsequent development and education depend is addressed in depth in the 1991 update of the Language and Language Impairments section of the National Strategic Research Plan.

Recent Accomplishments

Basic and clinical investigators in hearing and hearing impairment are undertaking research in many new directions. They are exploiting past accomplishments and taking advantage of the tools and insights offered by recent progress in neuroscience, cellular biology, immunology, molecular biology, genetics and computer technology. Progress in understanding the mechanisms of normal hearing is accelerating. However, transferring new knowledge into clinical applications is not occurring at a comparable rate.

The relatively slow rate of applying new knowledge to the problems of patients is due to many factors: the difficulty of the problems, the incomplete state of knowledge in the basic sciences, the lack of appropriate tools and models and the shortage of investigators bridging basic and applied areas. There is a severe shortage of clinical investigators who are conversant with the state-of-the-art research methods and their applicability to relevant clinical issues.

Hearing

Transduction and Homeostasis

Many insights into the function of the cochlea have been derived recently from in vivo and in vitro studies. Considerable progress is being reported in the measurement of cochlear blood flow and the study of its regulation. Studies of the composition, production, circulation and absorption of endolymph (the fluid in the membranous inner ear) are providing insights into the regulation of the properties of this unique fluid as well as the effects of these properties on transduction. Immunohistologic techniques have been employed and allow for an in-depth characterization of the inner ear. New research has shown that changes in hearing are associated with the loss of outer hair cells. Scientists have learned more about stereocilia and how they are physically linked at their tips and participate in frequency selectivity or tuning.

In vitro studies of isolated hair cells have led to a greater understanding of the biophysics of mechanoelectrical transduction and of ion channels in hair-cell membranes. Progress has been made in the molecular and functional characterization of the structural and contractile proteins of stereocilia, hair cells and the cuticular plate. This knowledge contributes to a better understanding of how stereociliary stiffness and hair-cell micromechanics are modulated.

Important progress has been made in understanding fast and slow motility of the outer hair cell. Stimulus and response characteristics have been detailed and provide clues about the function of these mechanisms in vivo. Biochemical studies have revealed the presence of second messenger molecules in outer hair cells, which may play a role in their slow motile mechanisms. Modern immunohistochemical techniques have shown the presence of more than one neurotransmitter at hair-cell synapses and are being used to identify the proteins associated with ion channels. Characterization of the membrane properties of sensory and neuronal elements using in vitro biophysical approaches is beginning to provide an understanding of the molecular basis of auditory function. For example, the ion-channel basis of electrical resonance has been elucidated in hair-cell membranes of several species. Ultrastructural studies have revealed details about the contact zones between outer hair cells and efferent nerve fibers. In addition, cells and tissues from the inner ear can be grown in tissue culture and hence are available for in vitro studies.

Recent studies of basilar-membrane motion and receptor potentials in the intact animal have led to a finer appreciation of the active process responsible for cochlear frequency selectivity. In certain species, including the human, the hearing organ generates sound spontaneously or in response to acoustic stimulation. In humans, these otoacoustic emissions are produced by outer hair cells and have great promise for practical diagnostic use to identify hearing loss.

Sound Processing in the Brain

Auditory nerve fibers connecting hair cells to the cochlear nucleus in the brain stem have been identified with intracellular marking techniques. New information is also available concerning the transformation of auditory nerve input in the cochlear nucleus. The membrane properties of some of these cochlear nucleus cells have been analyzed with in vitro techniques that allow the manipulation of the electrical and chemical environment and subsequent intracellular staining to elucidate cell morphology including the arborization of the entire axon. There has been substantial additional progress in understanding the encoding of complex signals transmitted from the auditory nerve to the cochlear nuclei. The relationship between the neural code for sound intensity, frequency and temporal characteristics and the perception of these stimulus variables has been further clarified. Chemical neuroanatomical studies have successfully used immunocytochemical, neurochemical, neuropharmacologic and molecular techniques to identify many of the neurotransmitters and receptors involved at specific synapses in structures throughout the auditory neural axis, especially with respect to the cochlear nuclei and the efferent feedback to the inner ear. The mapping of transmitter-receptor subtypes in the central auditory system has been initiated.

Research conducted in the central nervous system has produced exciting new findings. Progress has been made in understanding the structure and function of efferent feedback pathways to the inner and middle ears. There is now good evidence that both systems aid in the detection of signals in noisy environments, and there is the possibility that both may serve to protect the ear from acoustic injury.

Changes in the central nervous system have been described in response to enriched and deprived acoustic environments. New insights have been generated with respect to how the brain performs complex computations to create maps of auditory space and how these maps interact with visual space.

Auditory Perception

Recent research in auditory psychophysics has produced a set of working models of auditory perception that far exceed the bounds of the simple "energy detector" models of hearing in general use. Research under way in a variety of areas is providing remarkable advances in the understanding of how human and non-human listeners make sense of the auditory world around them, that is, how they assign identities and sources to the sounds they perceive and how they recognize the communication sounds of single and multiple speakers. This research provides the essential link that will enable the application of advances at the molecular, anatomic and physiologic levels to the design of improved auditory prosthetic devices.

There have been a number of exciting recent advances in the linking of psychoacoustical and physiological research. Behavioral measures of frequency selectivity have been developed that allow comparison with electrophysiologic measures of auditory tuning. These measures can now be used to characterize normal and impaired hearing, and the potential exists for the diagnostic application of such measures. Perceptual evidence of the role of various populations of auditory nerve fibers in coding sound intensity has recently been obtained. The influences of adaptation and active cochlear processes on perception have been elucidated in psychophysical tasks.

Increased understanding of the perception of spectral shapes and the ability of the ear to distinguish changes in shape from changes in intensity have been achieved. Spectral shape cues are used to distinguish many classes of speech sounds and contribute to auditory localization. Studies on the role of across frequency-band enhancement and interference effects on the detection and localization of sounds are providing improved understanding of complex "real-world" auditory perception.

New approaches are being used to characterize auditory localization by humans. Sounds presented over headphones can now provide the perceptions found in real auditory space, particularly when head movements are accounted for. These results provide new possibilities for presenting sounds in simulated situations and through prosthetic devices.

Increased study of the role of perceptual learning, selective attention, auditory memory and streaming in the formation of auditory percepts has contributed to the understanding of how we attend to multiple sound sources in complex acoustic environments.

Regeneration of Sensory Cells

Decades ago, it was shown that production of sensory cells in the ears of mammals ceases before birth. This finding confirmed that sensory cells are produced only during embryonic development and meant that damage to sensory cells later in life was irreparable. This fact is the basis for considering sensory hearing impairment as a permanent and irreversible condition.

It is now known that sensory cells are continually being added to the functional populations of cells in the ears of cold-blooded animals. Even more recently, it was shown that sensory cells can be regenerated in damaged cochlear epithelia in juvenile birds in which the production of these cells normally ceases early in embryonic development. This regenerative potential has been confirmed in several species and is not limited to immature animals. The results have provided an opening to understanding and perhaps manipulating the growth of human sensory cells.

Hearing Impairment

Hereditary Hearing Impairment

The genes causing a number of syndromes that involve hearing impairment have now been mapped. Recent accomplishments include the mapping of an Usher syndrome (deafness, vestibular loss and blindness due to retinitis pigmentosa) type 2 gene to the long arm of chromosome 1 and a gene for Waardenburg syndrome (deafness and pigmentary and integumentary changes) type 1 (WS1) to the long arm of chromosome 2. More than one gene is involved in both of these syndromes. At the same time, considerable effort is being expended to isolate the two genes that have been mapped. Comparative mapping suggests that WS1 is homologous to the Splotch gene in the deaf mouse.

Analyses of a large Costa Rican family in which many members have progressive low frequency hearing loss recently allowed the mapping of a gene for an autosomal dominant nonsyndromic form of hearing impairment to the long arm of chromosome 5. Other families with similar audiometric findings can now be tested to determine whether the same gene causes their impairment.

At least 28 X-linked (sex-linked) disorders involve hearing loss. Recent accomplishments include precise location of the gene causing albinism-deafness and tentative evidence of more than one X-linked gene for clinically identical forms of progressive mixed deafness. The gene for Alport syndrome has been located to the same region as one of the collagen genes (COL4A5). Further studies of several individuals with Alport syndrome suggest that mutations in the collagen gene cause this syndrome. It is of interest to note that hearing loss is associated with other syndromes caused by collagen defects, such as Stickler syndrome (COL2A1) and one form of osteogenesis imperfecta (COL1A1).

The development of human and animal cochlea-specific cDNA libraries is proceeding rapidly.

Acquired Sensorineural Hearing Loss

The role of genetic factors in disease processes that would otherwise be considered acquired has been underscored by the recent demonstration of a genetically controlled mitochondria defect which predisposes to aminoglycoside ototoxicity.

Similarly, mouse models of genetically induced sensorineural hearing loss of late onset may provide a better understanding of the genetic predisposition to presbycusis. The recent elucidation of the nature of a variety of afferent and efferent neurotransmitters will provide better understanding and possible therapy for sensorineural hearing loss. For example, the discovery of a variety of oncogenes associated with various tumors holds promise for better understanding of the development and growth of acoustic neurinomas and other tumors of the temporal bone. New insights into the prevention and treatment of ototoxicity may result from studies of pharmacologic blocking of ototoxic actions of various drugs. A better understanding of how ototoxic metabolites may cause damage to the cochlea may provide new insights into prevention and treatment of this problem.

Application of new immunobiologic techniques will provide an understanding to the normal and disrupted immune mechanisms responsible for damage to the inner ear in immune-mediated disorders. Recent evidence suggests that some individuals with progressive deafness have autoantibodies directed against inner-ear proteins. These studies open up avenues for the diagnosis of treatable forms of sensorineural hearing loss. Better techniques to diagnose perilymphatic fistulae might emerge from the findings of recent studies, suggesting a specific inner-ear protein may be detectable in perilymph that is not found in serum, cerebrospinal fluid or middle-ear fluid.

Recent developments of animal models for bacterial and viral infections, such as bacterial labyrinthitis, congenital cytomegalovirus infection and other viral infections holds promise for the development of new diagnostic and treatment modalities for sensorineural hearing loss caused by infections. In particular, recent developments in antiviral therapy hold promise for the treatment of inner-ear viral infection. Studies of biochemical factors including enzymes and the susceptibility of developing animals to ototoxic drugs will help clarify the unique susceptibility of the immature human to ototoxic drugs.

Otitis Media, Otosclerosis and Other Middle-Ear Disorders

Otitis Media

The most common cause of hearing loss in children is otitis media. Primarily a disease of infants and children, otitis media produces sequelae that may affect hearing later in life.

During the past three years, there has been important progress in understanding the epidemiology and pathophysiology of otitis media, and this progress has led to advances in prevention and treatment. This research has led to new questions and has revealed pathways for more detailed investigation.

Research in epidemiology and natural history indicates that otitis media forms a continuum of clinical and pathologic entities from acute, self-limited disease to chronic forms with destruction of middle-ear structures. Many persons affected with otitis media do not display clinical symptoms and ordinarily would go undetected. Several risk factors for acute otitis media and otitis media with effusion have been identified using multivariate models, and a genetic basis for otitis media has been suggested.

Research on eustachian-tube and middle-ear physiology and pathophysiology has provided new information on a surfactant-like substance, mucociliary clearance, neural connections between the middle ear and brain stem, tubal muscles, tubal compliance and effects of pharmacologic agents and adenoidectomy on tubal function.

Anatomic, pathologic and cellular biologic research has revealed the importance of cellular regulation and differentiation and receptor expression in the pathogenesis of otitis media. Developmental changes in tubotympanic anatomy have been recorded, and ultrastructural changes of the tubotympanum have been studied in normal and several pathological conditions. The application of immunocytochemistry to the study of the pathogenesis of otitis media has led to characterization of filament proteins, neuropeptides, oxidative enzymes, immunocompetent cells and inflammatory mediators. In addition, cellular patterns of middle-ear alteration, including epithelial metaplasia and migration and bone-cell activation, have been identified.

Microbiological, immunological and biochemical research has yielded additional evidence that upper-respiratory viral infections contribute to a high proportion of acute episodes of otitis media. The importance of the interaction between respiratory viruses and bacterial infection in the pathogenesis of otitis media has been revealed by human and animal studies. Research at molecular and cellular levels has begun to characterize cell-membrane receptors for bacteria causing otitis media and to reveal the contribution of bacterial cell-envelope products in middle-ear inflammation. Evidence suggests that the middle-ear immune response can be manipulated by donor T-lymphocytes from animals presensitized by oral antigen. Research has suggested that the presence or absence of an impaired immune response to certain bacterial antigens may allow differentiation between otitis media-prone and normal children.

Improving the immunogenecity of pneumococcal polysaccharide antigens and identification of common nontypable *Haemophilus influenzae* antigens have been primary goals in vaccine development for prevention of otitis media. The development, licensing and widespread use of *Haemophilus influenzae* type b polysaccharide-protein conjugate vaccines beginning in infancy is causing a major reduction in bacterial meningitis, which is an important cause of acquired sensorineural deafness.

Important progress has been made in the biochemical and molecular characterization of middle-ear inflammation including the role of bacterial products and host responses. Molecular studies have explored the bacterial genome that is related to adherence and antibiotic resistance.

Clinical research has yielded important progress in the screening and diagnosis of otitis media and has improved the medical and surgical management of otitis media. Advances in tympanometry have resulted in improved terminology and objective parameters. Bacterial surveillance has revealed changing patterns of bacterial resistance among the microorganisms that cause otitis media. The pharmacology of antibiotics used in the treatment of otitis media and their distribution into and out of the middle ear have become the subjects of intense investigation. Surgical prophylaxis and chemoprophylaxis of recurrent acute otitis media have been explored in several recent studies.

Otosclerosis and Other Middle-Ear Disorders

The understanding of otosclerosis and other types of conductive hearing losses due to infection or trauma has advanced in recent years. Using immunohistochemical and ultrastructural techniques, viral antigens of rubella and rubeola have been identified in otosclerotic tissues. These findings suggest that childhood viral infections may play a role in the genesis of otosclerosis. Recent ultrastructural studies have further elucidated this unique disorder of localized bone remodeling.

Advances have occurred in the development of biocompatible implants for the replacement of middle-ear ossicles. Additionally, there has been progress in the development of implantable or partially implantable hearing aids.

Assessment, Diagnosis, Treatment and Rehabilitation

Considerable progress has been made in the technology of hearing aids and auditory prostheses. Digital and programmable hearing aids with vastly increased potential for signal processing are being developed and fitted clinically. Programmable hearing aids permit much more precise fitting of hearing aid characteristics on the basis of individual needs than is possible with nonprogrammable hearing aids. In addition, a variety of noise-reduction schemes are being incorporated into hearing aids, ranging from those that vary the frequency response as the background noise spectrum and level change to those that process the outputs of arrays of microphones.

The multichannel cochlear implant has become a widely accepted auditory prosthesis for both adults and children.

The vast majority of adult implant recipients derive substantial benefit in conjunction with speechreading, and many can communicate effectively without speechreading. Some implanted children, including the prelingually deaf, derive substantial benefit, particularly with continued use. New sound processing techniques based on high-rate, nonsimultaneous (interleaved), pulsatile stimulation have been shown to improve the effectiveness of cochlear implants. A neural prostheses for insertion into the cochlear nucleus of the brain stem has provided encouraging levels of speech reception in individuals who have had bilateral destruction of the nerves of hearing caused by bilateral acoustic neurinomas or head trauma.

Studies of methods of tactual communication used by deaf and blind persons demonstrate the capacity of the skin and the proprioceptive system to provide a secure basis for the development of tactile aids. Such aids could serve as effective alternatives to powerful hearing aids and auditory prostheses.

Recent accomplishments in the area of auditory rehabilitation include use of computer-controlled video and audio laser disc systems for fully or semi-automated instruction, development of connected discourse tracking procedures for speech reading instruction, efficient enhancement of speech perception and increased understanding of the contributions of context and prior knowledge to the perception of spoken language from impoverished sensory input.

The areas of assessment and diagnosis have benefited from numerous developments in recent years, including development of noninvasive methods for measurement of the acoustical properties of the external and middle ears (acoustic immittance), that permit precise assessment and diagnosis of middle-ear disorders and disorders of discrete portions of the central auditory pathways, computer-based techniques for assessment of sound-evoked electrical activity in the cochlea (electrocochleography) and in the brain (auditory brain stem and cortical responses) and discovery and exploitation of spontaneous and induced emissions of sound from the inner ear (otoacoustic emissions). Measurements of otoacoustic emissions holds great promise for precise evaluation of defects within the inner ear and early identification of hearing impairments in infants.

Program Goals

Research to alleviate hearing impairment has yielded impressive results and promises to provide greater insight into how hearing disorders may be treated more effectively.

The prevention, diagnosis, treatment and rehabilitation of hearing disorders depend on the identification of the disease process, an understanding of its underlying basic mechanism and the development of effective intervention and rehabilitation strategies. Success in these endeavors requires close integration of research on hearing and hearing impairment.

An increasing number of new and evolving technologies will be applied to the elucidation of normal hearing processes, particularly those concerned with how speech and other biologically meaningful sounds are understood.

Further understanding of the mechanisms of normal hearing and hearing impairment rests on the synthesis of numerous factors: from understanding the physics of sound and the ear, through identifying molecular events at the cellular and subcellular levels, to analyzing the processing of sound information in the auditory nervous system and learning how these activities and interactions result in the perception of sound and the understanding of speech.

A multidisciplinary approach to the study of hearing is required to interpret these complex processes. In fact, improved understanding of hearing mechanisms have resulted from the integration of strategies and technologies from a wide variety of fields. As this research is validated by ongoing investigation, clinical applications are being developed to enhance patient care.

Progress in key areas offers special opportunities to enhance prevention, diagnosis and treatment of many of the disorders that cause hearing loss and deafness. Pursuit of these opportunities will reduce the incidence and prevalence of hearing impairment.

Research in hearing and hearing impairment requires a multidisciplinary base and accelerated integration of basic knowledge with clinical needs. The broad objectives of the hearing and hearing impairment research program include the study of normal mechanisms and disorders that disrupt auditory function.

Goals of research on hearing should include:

- Determination of how the ear processes and encodes sound.
- Determination of how the central nervous system processes the output from the ear.
- Determination of how central nervous system processing leads to perception and behavior.
- Characterization of the life cycle (development, maturation and aging) of the normal auditory system.

Goals of research on hearing impairment should include:

- Development of population studies to determine and track the incidence, prevalence and risk factors of hearing impairment and ear disease.

- Initiation of multidisciplinary studies to determine the pathogenesis of specific hearing disorders and ear diseases.
- Mapping, isolating, cloning, sequencing and characterizing the genes responsible for hearing impairment.
- Performance of clinical trials to establish the efficacy of existing and new treatments for hearing impairment and ear disease.
- Development and improvement of devices and rehabilitative strategies to assist people with hearing impairment and tinnitus.
- Development of professional and public educational strategies to prevent hearing impairment and ear disease.

Research with Multicultural Populations and Women

The range of scientific and clinical concerns encompasses the pluralistic character of society, as well as the demographic projections for the nation. Whereas minority groups suffer from the same types of hearing impairments as nonminority groups, there are some pertinent differences in prevalence, causes and manifestations of communication disorders that merit research. There is a need for epidemiologic information on the incidence, prevalence and risk factors of hearing impairments in multicultural populations. Otitis media has a higher incidence in American Indians and Alaskan Natives and a lower incidence in African Americans than in the population at large. Although various explanations have been offered, ranging from cross-racial differences in eustachian-tube structure and function to differences in general health status, there is no definitive evidence for these explanations. There is some evidence that African Americans may be less susceptible to hearing loss from noise exposure than other racial groups, although additional research is needed to substantiate this observation. The elderly African-American population has a lower prevalence of tinnitus than the elderly population at large. The reasons for these differences are not known. There is a need for further research on the impact of socioeconomic, educational and cultural factors on hearing impairment.

Research is needed on multilingual factors that have an impact on speech perception. For example, the effect of hearing impairment on speech understanding may be greater for individuals who are raised in bilingual environments than in environments where only English is spoken. There are no known racial differences in terms of the basic mechanisms involved in encoding and processing of sound. Some diseases of the ear may vary between the sexes. Otosclerosis, for instance, has a greater prevalence in females, whereas some studies suggest that males are more likely to develop Meniere's disease. The reasons for these gender differences in susceptibility to certain ear diseases are not known.

Research Opportunities, Strategies and Priorities

The understanding of any disease or impairment requires basic knowledge about how the affected system functions in its normal state. In search for this knowledge, auditory scientists have recently made some fundamental discoveries. Exploitation of these discoveries during the next few years promises to provide essential new information about how the auditory system is organized and functions. Areas that offer particularly strong opportunities for progress are discussed below.

Hearing

Transduction and Homeostasis

Mechanoelectrical Transduction Mechanism of Hair Cells

The key step in the function of the ear is the transduction of mechanical stimuli into electrical responses that can be synaptically forwarded as neural impulses to the brain. Several lines of experimental evidence indicate that inner hair cells effect this function by a unique transduction process in which stimuli directly gate the opening and closing of mechanically sensitive ion channels. This direct mechanism of transduction raises the possibility of reciprocal interactions between a hair cell's electrical response and the mechanical properties of the cochlea. The use of solid-state microfabrication techniques, lasers, optical methods and other technologies offers the possibility of constructing probes for direct examination of the mechanical changes in the hair bundle during transduction and during adaptation to protracted stimuli. Similar techniques may also be used to make accurate measurements of the basilar membrane's properties and of the possible influence of hair bundles on basilar-membrane mechanics.

Role of Outer Hair Cells in Amplification and Tuning

The mammalian auditory system is an exquisite discriminator of the qualities of sound. Over the past several years, a wealth of information has accumulated which indicates that the basis of such acute frequency selectivity resides in the outer hair cells. Outer hair cells appear to enhance the mechanical input to the inner hair cells, the cells mainly responsible for the transduction of acoustic stimuli. Three plausible underlying mechanisms of this enhancement have been identified in the activity of the outer hair cells. These include fast voltage-dependent motility, slow metabolically dependent motility and interactions between stereocilia and the tectorial membrane.

At the system level, the elucidation of the contributions of each mechanism to enhanced transduction is a fundamentally important goal. While much basic information has been gathered either through modeling or in vitro approaches, the significance of these mechanisms in the intact, in vivo system must be addressed. There is a need to determine whether these mechanisms are capable of influencing cochlear micromechanics in the high-frequency region, where enhancement of tuning is acknowledged to be substantial. Modern techniques capable of measuring alternating-current and direct-current basilar-membrane motion in the high-frequency region are particularly useful, as are measures of otoacoustic emissions. However, strategies must be developed that transcend mere confirmation of the outer hair cells' importance in feedback schemes. There is a need to appraise contributions from each of the potential enhancement mechanisms of outer hair cells. In particular, the experimental exploitation of known temporal differences among the three mechanisms may be worthwhile.

On the cellular level, an understanding of the molecular mechanisms governing these outer-hair-cell mechanical phenomena is of special interest and will aid in the determination of microenvironmental factors which influence frequency discrimination. A notable example is the observation that cell turgor affects outer-hair-cell fast motility. There is little doubt that continued study of the outer hair cell's effector role, using both in vitro and in vivo approaches, will lead to a better understanding of normal and abnormal cochlear function.

Afferent Synaptic Signaling by Hair Cells

The ability to locate sounds in space relies on the precise encoding of responses to sounds arriving at both ears. To account for the observed ability to locate sounds, the afferent synapses that relay information from hair cells to auditory nerve fibers must operate with an unusually high temporal resolution. These synapses are morphologically unique, both in their presynaptic specializations and in their large number of postsynaptic elements. Appropriate physiologic experiments, especially those on new experimental preparations including pre- and postsynaptic elements, are needed to document and analyze the synapses' operation.

Pharmacologic, physiologic and molecular studies are needed to elucidate the nature of the afferent transmitter, the enzymes of its synthesis and the mechanism of its release. At the postsynaptic level, receptors and their subtypes should be identified as well as the ensuing physiological and biochemical processes. It is essential to focus on the characteristics of ion channels, G-proteins and second messengers associated with these receptors. Furthermore, biochemical modulation of pre- and postsynaptic processes need to be elucidated. The results will aid in the understanding of synaptic function and of coding in the eighth nerve.

Molecular Structure of Auditory Receptor Organs

The unique structure of the hearing organ is the basis for its function as a mechanotransducer. It encompasses elements that provide structural support for the receptor cells, the substrate for transduction and motility, and regulate the intracellular milieu. The integrity of these structural elements is essential both in transduction proper in inner hair cells and in regulatory feedback in outer hair cells. Past research has delineated many of the cellular and subcellular components of the structure that are responsible for normal and abnormal auditory function. Permanent losses of hearing sensitivity can result from small fractures at the bases of the stereocilia caused by exposure to intense sound. Although several of the component molecules of the stereocilia have been identified, many other stereociliary constituents, which are essential for hearing and probably unique to the inner ear, are as yet unidentified.

The mechanoelectrical transduction channels, the afferent synaptic bodies and the components of the subsurface cisternae of hair cells are other examples of unique but biochemically unidentified structural elements of the hearing organ. If there is to be an understanding of the molecular substrate of hearing, constituents that have been isolated by immunologic and electrophoretic methods need to be identified and functionally characterized. That knowledge is fundamental to theoretical frameworks for the development of new drug therapies that could be applied to such conditions as tinnitus and Meniere's disease and in the protection of the auditory system from damage induced by intense sound, ototoxic antibiotics and anticancer, chemotherapeutic agents.

Homeostatic Mechanisms in the Cochlea

Homeostatic mechanisms in the cochlea are processes that generate and maintain the natural environment in which transduction takes place. Supporting tissues and structures, such as the stria vascularis, Reissner's membrane, the basilar membrane and supporting cells of the organ of Corti participate in the homeostatic processes. Included are the maintenance of the ionic composition and electric potential of the extracellular fluids (endolymph and perilymph), the internal milieu of hair cells and supporting cells, the communication between cells by means other than synaptic mechanisms, the local control of blood flow to provide oxygen and nutrients and the local control of immune responses. While some of these mechanisms may reflect general physiologic principles, others may be unique to the cochlea. Endolymph, for example, is the only extracellular fluid with its particular ionic composition and electric potential.

Recent years have brought new information and theories on regulation of fluid composition, autoregulation of cochlear blood flow and cellular communication. In addition, research has begun to characterize molecular and cellular regulatory processes such as those involving ion channels and second messenger systems. A comprehensive understanding of the means by which the cochlea maintains its environment has not been achieved, and research should focus on the underlying regulatory mechanisms. This understanding is essential for a full appreciation of auditory processing, understanding disease processes and designing therapeutic approaches. Disorders of cochlear homeostasis and regulation may underlie a variety of disorders including sudden hearing loss, Meniere's disease, tinnitus and presbycusis. On the other hand, specific cellular processes may be involved in protective phenomena in the cochlea. For example, pre-exposure to moderate-level sound will protect the ear from some of the effects of traumatic noise exposure. The mechanisms of such long-term modulation of responses to acoustic stimulation remain to be elucidated.

There is a need to pay particular attention to:

- Regulation of the ionic environment of the cochlea.
- Regulation of the intracellular milieu of hair cells.
- Regulation of cochlear metabolism including hormonal and local influences; receptor mechanisms and the role of second-messenger systems.
- Intercellular communication.
- Local regulation of blood flow.
- Regulation of local immune responses.
- Modulation of responses to traumatic acoustic stimulation. Investigations into these topics require exploration of the system at all levels from molecular mechanisms to functional aspects.

Molecular Biology of the Cochlea

The recent advances in molecular biology afford powerful new techniques for investigation of the molecular bases of the various phenomena discussed above. Many of the important proteins of the cochlea may be identified and sequenced more efficiently by molecular cloning than through biochemical techniques. The identification of promoter and enhancer sequences for genes expressed in the cochlea should be valuable in elucidating the processes that regulate the development and perhaps the regeneration of cochlear cells.

At the same time, however, there are exceptional difficulties associated with molecular-biologic analysis of the inner ear. In particular, the small amount of cellular material in the ear severely restricts our ability to construct a complex, complete and specific cDNA library representing mRNAs for proteins important in mechanoelectrical transduction, synaptic transmission, ionic homeostasis and the other functions of cochlear cells. From the animals on which auditory experimentation is done, it would be useful to select a few species for which cDNA libraries can be made efficiently. In view of the laborious nature of library construction, it may be desirable to promote collaborative construction of libraries that will be accessible to investigators from numerous laboratory groups.

Beyond its utility in defining the proteins of the inner ear, molecular genetics offers the long-term prospect of gene therapy. Which genetic lesions of hearing can be meaningfully attacked by this means remains uncertain; it will first be necessary to isolate and characterize various genetic lesions and to ascertain in which cells mutant genes are expressed. Despite the long-term nature of this objective, it holds great promise that will steadily increase as new techniques for genetic therapy emerge throughout medicine.

Sound Processing in the Brain

Cellular Basis of Signal Processing in the Central Auditory System

Understanding the neural basis of hearing disorders requires an understanding of the cellular mechanisms involved in normal hearing. Neural impulses generated in the auditory nerve are processed by neuronal networks connected by synapses. Thus, the synapse forms the basis for mechanisms underlying acoustic information processing, the formation of neuronal circuits and response plasticity. Using a variety of chemical neurotransmitters and specialized receptors, synapses can transmit excitatory or inhibitory influences from one neuron to another. At synaptic junctions, pathologic and age-related changes may produce hearing impairment by alterations in the receptor sensitivity to and synthesis, degradation, uptake and release of neurotransmitters, as has been demonstrated in other regions of the brain. Understanding these changes may lead to the development of specific chemical blockers which can be of great practical value in basic research and ultimately lead to drug therapy to ameliorate certain kinds of hearing impairment.

At all levels of the auditory system, high priority should be given to studies of functional connections of neurons and synaptic mechanisms. Whenever possible, these studies should include:

- Identification and location of specific neurotransmitters and neuromodulators.
- Definition of receptor type.
- Understanding of transmitter-receptor interactions including ion channels and second messengers.
- Characterization of electrical properties of the cell membrane.
- Description of the size, source and distribution of different terminal types on the target cell's soma and dendrites.

These studies should exploit the wide range of existing and emerging methods of modern neuroscience using intact animals, tissue slices and isolated-cell preparations. A variety of approaches should be pursued, such as pathway-tracing techniques and promising new methods for trans-synaptic labelling. Other valuable approaches utilize intracellular staining to identify precisely the neurons under study and the use of genetic, molecular, immunocytochemical and pharmacologic probes. Application of these technologies to human material should be pursued wherever possible.

During the past decade, enormous technological advances have been made which permit high-resolution studies of neural circuits, subcellular components and even single molecules. Despite these advances, many basic questions remain to be answered. Long-term systematic studies addressing these questions will ultimately lead investigators toward an understanding of the mechanisms involved in normal auditory function and toward the successful treatment of hearing impairment.

Neural Basis of Auditory Perception

All acoustic information enters the brain as discharge patterns in the fibers of the auditory nerve. This incoming neural input is reprocessed in the brain stem into multiple parallel pathways, each of which may be specialized to extract different features of the acoustic stimulus, such as frequency content, temporal pattern, intensity, location in space, phonetic identity, etc. Each of the ascending pathways, in turn, may be controlled by descending pathways from higher centers, some of which may enable us to attend to certain features of a stimulus while ignoring others or help discern signals embedded in background noise.

In recent years, tremendous progress has been made in understanding the neural basis for auditory perception, especially location of sound, through a variety of classic and novel neuroanatomic, neurophysiologic and mathematical modeling techniques.

Such knowledge is necessary if there is to be understanding and effective treatment for complex, sensorineural hearing impairments. As knowledge of these phenomena increases, it should be possible to improve the ability of people with hearing impairment to hear in noisy environments, to improve the naturalness of sounds reproduced by earphones, hearing aids and cochlear prostheses and to create better interfaces between humans and computers in robotics and other sensing applications.

Although important progress has been made, the current level of understanding is very limited compared with what remains unknown. High priority should be given to the following areas of research:

- Studies of all levels of the auditory pathway to relate neuroanatomic and neurophysiologic findings to animal and human psychophysical observations, using similar paradigms and stimuli whenever possible.

- Complete anatomic and physiologic characterization of both afferent and efferent systems and description of the differences in response processing between anesthetized and unanesthetized, behaving subjects.

- Definition of the effects of aging on neuronal processing in those areas in which the normal system is well understood.

- Study of the potential for central reorganization subsequent to peripheral injury such as noise-induced hearing loss or central injury such as stroke.

- Investigation of the plasticity of the mature auditory system and the impact of modified input or experience on its organization. Ultimately, research in plasticity must be tied to human studies. This link may now be possible given the recent improvement in imaging techniques permitting the correlation of specific psychophysical deficits with well-defined anatomic defects in humans with lesions in the central auditory pathways.

The use of animal models will continue to be an important approach to understanding hearing and hearing impairment. In particular, a comparative approach that includes different animal models and the study of different hair cell systems (auditory, vestibular, lateral line and electro-reception) should be employed. Information from studies of this nature will add to the wealth of data that has been obtained during the past few years from animal models.

Mathematical Modeling of Auditory Function

Rapid advances in understanding the auditory mechanisms in the middle ear, inner ear and central nervous system permit the development of quantitative models for auditory function that are based on anatomical, physiological and psychophysical data. Many of these models have become feasible only with the advent of large-scale computer facilities. Specific examples of functions to be modeled include sound transmission in the middle ear; macro- and micromechanics of the inner ear; mechanical, electrical and electromechanical transduction by hair cells; active processes of neural control of transduction events; representation of speech-like stimuli in terms of auditory nerve discharges; distributed neural processing of auditory nerve discharges by cell groups in the central nervous system; sound location; and relationships between auditory neural responses and human auditory perception. These models are essential; they will provide concise descriptions of normal auditory function of groups of neurons that can be tested experimentally to relate to psychophysical and perceptual function and used to study abnormal systems. At the middle-ear level, this modeling can be used to predict outcomes of different approaches to surgical reconstructions of the middle ear. Neural models are also applicable to the design of coding strategies for inner-ear and more central prosthetic devices, and they could contribute to the development of computer neural networks simulating and perhaps augmenting brain function.

Auditory Perception

An essential component of understanding auditory function is the study of the process by which sound patterns are perceived. An overriding question is: "How are acoustic inputs to the ear converted into meaningful percepts in the mind of the listener?" To answer this question requires continued and expanded research efforts in three principal areas: (a) the psychophysics of sensory coding, that is, studies in both human and nonhuman subjects of the psychophysical manifestations of normal and impaired cochlear and neural processes; (b) the psychophysics of complex sound perception, that is, studies of the relationships between the physical properties of sound patterns and the perceptual properties of the resulting sensations; and (c) perceptual organization and cognition, that is, studies of the processes by which acoustic patterns are interpreted in terms of the location, identity and significance of the objects and events that produce them.

Psychophysics of Sensory Coding

As new discoveries are made about the structure and function of the auditory system, it will be essential to establish their relation to auditory perception. For example, a large body of data currently exists on frequency selectivity in human and animal subjects, yet little is known about how psychophysical measures of frequency selectivity reflect what is currently thought to be the underlying mechanism, such as outer hair cell function and the active processes in the cochlea. Definition of the auditory perceptual correlates of peripheral auditory function should lead to behavioral measures that go far beyond audiometry in characterizing the perceptual aspects of auditory function, as well as the intactness of the underlying auditory structures.

Opportunities for research in this area will include:

- Psychophysical studies aimed at defining perceptual correlates of peripheral and central auditory function, as well as the inverse (physiologic studies guided by psychophysical data and models, utilizing similarly complex signals).
- Psychophysical studies of the perceptual consequences of damage to the auditory system.

Psychophysics of Complex Sound Perception

Considerable progress has been made in understanding perception under conditions in which acoustic information is combined across several adjacent or remote spectral regions and over time. Beyond demonstrating that simple "within-critical-band" models of auditory function are inadequate, these studies provide a basis for understanding the perception of spectral shapes and will contribute to an understanding of complex "real-world" processes such as those involved in the perception of speech. Examples of this work come under such headings as "spectral profile analysis," "comodulation masking release," "dynamic properties of hearing" and "informational masking." Specific research opportunities include:

- Expanding our understanding of the ways in which acoustic information, from several spectral or temporal regions or from the two ears, combines to enhance or mask the perception of target sounds.
- Increasing understanding of dynamic and adaptive processes in auditory perception.
- Expanding our understanding of the ways in which the information content of complex sound patterns can enhance or interfere with detection and identification.
- Elucidating the connections between psychophysical performance and the perception of speech sounds, both in quiet and in the presence of competing signals.
- Developing descriptive and quantitative models to account for the perception of complex sound patterns.
- Increasing understanding of the ways in which sensorineural hearing loss affects these functions.

Perceptual Organization and Cognition

In recent years, there has been increased effort aimed at understanding how acoustic inputs are combined with prior knowledge and contextual information to result in the generation of meaningful percepts. This work has proceeded under such headings as "auditory streaming," "auditory scene analysis," "auditory object perception," "auditory perceptual learning," "selective and divided attention," "auditory memory," "auditory space perception" and "acoustic versus phonetic coding." This work has provided valuable insights into the separation of signals from noise, the perception of multiple inputs and the perception of speech. Its continuation and expansion are strongly encouraged. Specific research opportunities include:

- Expanding understanding of the acoustic properties of signals that allow them to contribute to unitary or multiple percepts.

- Expanding understanding of the ways in which both monaural and binaural inputs contribute to decisions about the direction and location of a sound source in both humans and animals.

- Experimenting on the integration and separation of several sources of information, both intramodally and cross-modally.

- Developing descriptive and quantitative models of perceptual organization.

- Relating emerging knowledge about perceptual organization to the development of a comprehensive model for perception of acoustic communication signals.

- Extending perceptual organization and modeling by including animal models to provide an understanding of the perceptual consequences of sensorineural hearing impairments and auditory perceptual disorders.

- Integrating an understanding of perceptual consequences of sensorineural hearing impairments and auditory perceptual disorders with emerging physiologic understanding of central auditory processing.

Development, Aging and Regeneration

Development of the Auditory System

The development and maturation of normal hearing and the auditory problems of children are now appropriate subjects for systematic and comprehensive investigation. The molecular genetic basis of normal and abnormal auditory structure and function should be studied in animal models and humans:

- Research on embryonic mechanisms for the formation of the normal ear and the auditory pathways of the brain will lead to an understanding of mechanisms that produce congenital defects and approaches toward correction.

- The importance of critical periods for functional development and changes in the strength of interactions and interdependencies in the auditory system are likely to be related to changes in susceptibility to hearing loss.

- Influences of environmental factors through several stages of auditory development should be evaluated. Metabolic, biochemical and immunological changes in the middle ear, the inner ear and the brain that occur over the lifespan should be investigated.

Although there is adequate information on developmental aspects of sensitivity within the auditory system, understanding of other perceptual attributes is not well documented. Insights into the auditory abilities of infants and young children are needed. It is vital to appreciate the other complex developmental processes that underlie speech perception so the growing potential for early diagnosis and treatment of all auditory disorders can be made.

This research should be integrated with studies characterizing the mechanisms that are responsible for cell proliferation and differentiation in the cochlea. It is likely that similar mechanisms are responsible for the induction of sensory cell regeneration and recovery of hearing found after trauma in nonmammalian auditory systems.

The survival of neurons is dependent upon their connections with sensory cells, so the loss of receptors can result in the loss of auditory neurons. Cochlear implants depend upon surviving neurons for their prosthetic efficacy. Recent studies suggest that electrical stimulation may prevent progressive neural degeneration in congenital or early acquired profound hearing loss and that nerve terminal regeneration can occur under certain conditions. The mechanisms underlying these processes should be defined through further research and applied to enhance the efficacy of cochlear prostheses.

Age-Related Changes in Hearing

Age-related hearing loss is a complex state which reflects, to a large extent, changes throughout the entire auditory system. All mechanisms for acoustic transduction, transmission and perception must be considered in light of the aging process. One hallmark of age-related hearing impairment is an unexplained loss in speech understanding without a concomitant loss in sensitivity. Progress in elucidating all of the aspects of age-related hearing loss will result from our ability to study peripheral and central components in humans while developing appropriate animal models. Studies in humans should include behavioral, electrophysiologic, neuropathologic and molecular measures of aging. Animal models will be particularly useful in elucidating genetic controls of age-related hearing loss. Moreover, animal models can be correlated with human results to provide a framework for the changes observed with age.

Since many factors contribute to age-related hearing loss, studies in structural changes in the cochlea and central auditory pathways, homeostatic mechanisms of the inner ear, environmental and genetic effects on hearing, and psychologic bases of perception and recognition will contribute greatly to understanding and prevention.

Regeneration of Sensorineural Elements and Accessory Structures

Sensorineural hearing loss has long been considered irreversible because the production of the permanent sensory and nerve cells in the inner ear normally ceases before birth. However, recent animal research has shown that under certain conditions, sensory cell production can be reactivated in mature damaged ears. It is also known that these regenerated cells contribute to a recovery of hearing. Study of the molecular control and the cellular mechanisms of this self-repair process is possible with the methods of modern biotechnology. Elucidation of the basic processes should lead to therapeutic advances. It is reasonable to expect that the molecular events that stimulate progenitors cells to regenerate will be identified within the foreseeable future. This identification will allow the development of pharmacologic agents for controlling cell replacement and auditory recovery. Research in this area should:

- Identify molecular events that evoke proliferation leading to the replacement of lost sensory cells.

- Assess the roles of known and suspected growth factors that may influence both the production and development of replacement sensory cells and the formation and maintenance of their contacts with neurons.

- Explore the underlying mechanisms for the induction and regulation of postnatal sensory cell regeneration and differentiation. Encourage the application of this knowledge so that the mammalian cochlea and vestibular system could be artificially induced to undergo regeneration or self repair.

- Investigate the basis for the recent discovery of additional sensory cell production evoked in the embryonic mammalian cochlea and explore the potential for spontaneous sensory cell regeneration in the auditory and vestibular systems of postnatal mammals.

- Assess the contributions of various other potential repair processes in the ear, including repair of damaged subcellular components of hair cells and repair of damaged links between sensory cells and the overlying tectorial membrane.

- Evaluate mechanisms leading to the reformation of neuronal connections in the hearing organ and their functional recovery.

A multifaceted approach, which includes biochemical, cellular, physiological and behavioral investigations, is necessary to understand fully the complex processes that underlie restoration of auditory function. The realization of clinical gains from this research is likely to require years of sustained investigation, but the potential benefits are great. For 80 percent of the more than 28 million Americans affected by hearing impairment, their loss is currently irreversible due to inner-ear hearing impairment. The studies proposed here suggest that this type of hearing impairment may not have to be considered permanent.

Hearing Impairment

Hereditary Hearing Impairment

More than 300 hereditary disorders cause hearing impairment. Many forms of hereditary hearing impairment result from the actions of more than one gene.

The rapid identification over the past few years of large numbers of DNA markers showing considerable variation among individuals and spanning most of the human genome has provided the framework for locating genes whose protein products are unknown. The discovery of the polymerase chain reaction (PCR) for amplifying DNA segments has played a major role in the rapid accumulation of these informative markers. The potential to map genes involved in hearing impairment now depends on obtaining sets of families in which the same mutation causes the disorder in affected members. However, clinically identical disorders are not necessarily due to the same gene. In fact, more than 40 genes are estimated to cause autosomal recessive early-onset deafness.

High priority should be given to the identification of families suitable for mapping genes that cause hearing impairment. International collaborations and the establishment of consortia for studying specific disorders are essential for this effort. The establishment of a data base of families with probable hereditary hearing impairment, willing to participate in genetic studies, will require the active participation of clinicians who can provide complete and accurate diagnostic information. Gene mapping is most likely to result from the analysis of data collected from a large pedigree in which there are many family members with autosomal dominant patterns of hearing impairment transmission and from sets of related families (such as those in isolated populations) with autosomal recessive forms of hearing impairment transmission. In these sets of data the problem of genetic heterogeneity is minimized as the same gene is likely to cause the disease in all affected family members. Both syndromic and nonsyndromic forms of hearing loss should be studied.

Advances in comparative mapping of the human and mouse genomes promise to be valuable in identifying human genes. Since there are extensive regions of homology, locating genes for hearing impairment in the mouse indicates a likely chromosomal location for similar genes in humans and suggests candidate genes. DNA markers spanning the mouse genome are being developed, and the use of different species and subspecies to map mouse genes is proving fruitful. Many mouse strains with hearing loss are available through federally supported laboratories. Several deafness genes have been located in humans and mice, and progress toward isolating and chemically characterizing these genes should be rapid.

Auditory assessments that differentiate carriers of recessive genes for hearing impairment from noncarriers would be most useful. Parents of affected individuals are obligate carriers; and, as an adjunct to the gene mapping studies in humans and mice, the hearing of obligate carriers and normal controls should be measured.

The successful mapping of a hearing impairment gene provides useful information for early detection of affected individuals and for identifying carriers of the gene. Locating the gene on a chromosome allows isolation, cloning, sequencing and determining the mutation and its protein product. The way in which the protein product produces the hearing impairment in the inner ear can be determined, and the counterpart gene and its protein product can be determined. The role of its product in development or maintenance of the inner ear can be determined. New technology, including the development and screening of inner ear-specific cDNA libraries, will facilitate the breakthroughs in defining the genetic basis of hearing impairment. Successful treatment and prevention of genetic hearing impairment may eventually be achieved by introducing normal genetic material into affected cells. The technique of gene therapy, which is already being applied to other genetic disorders, is likely to become an option for the prevention or amelioration of hereditary hearing impairment.

Studies of hearing impairment in which a genetic and an environmental component are suspected, should be carried out. Epidemiologic studies on hearing disorders are needed to augment available data on incidence, prevalence and risk factors. Data on multiple variables, including age, gender, ethnicity, trauma, drugs, toxins, infections, smoking, diet, genetic markers (particularly those involved in the immune system), autoimmune diseases and congenital malformations, should be analyzed for etiologic clues. In some instances, an environmental cause will be more likely. When there is evidence of a familial component to the hearing impairment, extensive and detailed family history information should be obtained on first and second degree relatives. Many different measures of auditory function should also be obtained on family members, including pure-tone audiometry, spondee threshold, speech recognition thresholds, tympanometry, measurement of acoustic reflexes, electrocochleography, auditory brain stem response and otoacoustic emissions, as well as imaging studies. These data may contribute to the genetic analysis of the hearing disorder. Hypotheses of dominant, recessive, sex-linked, polygenic and mitochondrial inheritance should be examined.

In summary, research priorities to better understand the genetic basis of hearing impairment include:

- Map, isolate, clone, sequence and characterize genes responsible for hearing impairment in humans and animals.
- Solicit the participation of families in studies of hereditary hearing impairment. Educate professionals serving people with hearing impairment regarding selection criteria for such families.
- Develop clinical and physiological tests which identify individuals with hereditary hearing impairment and carriers of recessive genes for hearing impairment.
- Develop comprehensive inner ear-specific cDNA libraries in humans and laboratory animals.

Acquired Sensorineural Hearing Loss and Environmental Influences

Role of Genetics in Acquired Hearing Loss

A number of disorders which result in acquired sensorineural hearing loss may have a genetic basis which predisposes the individual to the deleterious effects of environmental factors. These include susceptibility to noise-induced hearing loss and drug ototoxicity. Degenerative disorders such as presbycusis may also have a genetic basis. Studies using molecular genetics and related techniques should define these disorders better.

Infectious Diseases Affecting Cochlear Function

Maternal Cytomegalovirus Infection and Hearing Loss in Children

It is estimated that one percent of all children born in the United States contract maternal cytomegalovirus (CMV). Ten percent of these children are born with mental retardation and hearing loss. Fourteen percent develop hearing loss alone, which may not become apparent until years later. It is possible that CMV-related hearing loss in children may have a greater incidence than suspected. Research is needed to devise effective screening techniques to detect CMV infection in the newborn. Studies are needed to investigate the pathophysiology of CMV infection in the developing inner ear of the fetus in comparison to CMV infection in the adult inner ear. Research on genetic or environmental factors that may predispose a developing fetus to CMV infection are needed. Since not all newborns exposed to CMV develop hearing loss, there is a need to determine if certain factors predispose the inner ear to damage as a result of CMV infection. High priority should be assigned to the development of strategies to prevent CMV-induced congenital deafness.

Postnatal Infections

Sudden sensorineural hearing loss may be caused by a viral infection. Further study is needed of putative viral pathogenesis of this and other inner-ear disorders. Diagnostic techniques, such as serology, immunohistochemistry, microbiology and molecular biology, should be explored in greater detail. Bacterial meningitis, such as that caused by the pneumococcus, results in a high incidence of acquired sensorineural hearing loss. Additional research is needed to determine the mechanism and the locus of the auditory pathway damaged by meningitis. The development of vaccines and the evaluation of their efficacy are essential.

Treatment with corticosteroids and antibiotics may reduce the incidence of sensorineural hearing loss in patients with bacterial meningitis. The role of the inflammatory and immune process in meningitis may therefore have a major impact on the outcome of hearing in these patients. Animal models of meningitis are needed, and new treatment modalities should be tested. Clinical trials of the treatment of patients with meningitis are needed.

The effect of viral meningitis on the auditory system should be studied. Delayed sequelae from viruses are known to occur in infections of the central nervous system, and their role in auditory system dysfunction can be presumed but should be substantiated. Particular attention should be focused on latent viruses of the Herpes group, which have been implicated in several inner-ear and eighth cranial nerve disorders, such as Meniere's disease, vestibular neuronitis and Ramsay Hunt syndrome.

Fungal meningitis may produce sensorineural hearing loss, particularly in patients who are immunosuppressed, including patients with acquired immunodeficiency syndrome (AIDS) and transplant patients. The mechanisms of damage to the auditory system should be further delineated.

Auditory Consequences of Acquired Immunodeficiency Syndrome

Infection with human immunodeficiency virus (HIV) can result in AIDS, characterized by immunosuppression, the presence of Kaposi's sarcoma and a high level of opportunistic infections. HIV infection can also lead to AIDS-related complex (ARC), which is part of the clinical spectrum of this disease but has a lower incidence of opportunistic infections. Both AIDS and ARC are associated with sensory and neural complications that include hearing impairment. It is estimated that 75 percent of adult AIDS patients and 50 percent of ARC patients develop hearing loss.

The cause of auditory system changes in HIV-positive patients is unknown. Direct infection of the central nervous system by HIV is well documented, and strains of the virus are known to infect selectively specific neural populations. Hearing disorders in AIDS patients could be caused by HIV infection of the inner ear or the central auditory system. Many of the complications of AIDS, however, are the result of opportunistic infections rather than of HIV itself. By far the most prevalent co-pathogen is CMV, with more than 90 percent of AIDS patients having CMV infections. Since CMV is known to damage the auditory system preferentially in congenital infections, it seems likely that CMV is involved in HIV-related auditory lesions as well. Research to clarify the role of HIV and CMV infection in the auditory systems of AIDS patients should lead to improved strategies for treatment of hearing impairment in AIDS.

Some drugs that have been used to treat AIDS or infections which occur in AIDS have caused temporary or permanent hearing loss. Research needs to be done to investigate the mechanism underlying this hearing loss and the ototoxic potential of drugs being developed in the future to treat AIDS patients.

The use of new antiviral agents in AIDS patients with sensorineural hearing loss will be an area of high interest. Studies of the mechanisms of action of these antiviral agents in preventing or reversing hearing loss in AIDS will be important and have far-reaching implications for treating viral infections of the inner ear in the general population.

Neoplasia

The natural history, genetics, presence of hormone receptors and factors controlling growth should be studied further in neoplastic disorders, such as acoustic neurinoma (vestibular Schwannoma) and chemodectoma (glomus tumors). The incidence of acoustic neurinomas is higher at autopsy than in patient populations implying that the growth rate of these tumors may be extremely slow in some patients. Methods of treatment are controversial, and multi-institutional trials are needed to address questions about radiation, medical and surgical treatments.

Squamous cell carcinoma of the external ear appears to be related to exposure to the sun. The role of environmental factors, including depletion of the ozone layer, should be investigated. The etiologic factors underlying squamous cell carcinoma of the middle ear and mastoid should be elucidated. Multi-institutional, well-controlled trials of surgical, radiation and medical therapy need to be carried out to improve survival. Improvement in survival of patients with rhabdomyosarcoma who receive multimodality therapy has been achieved.

Age-Related Changes in the Cochlea

Presbycusis or age-related hearing loss is the most prevalent and least studied disabling condition. Although long life is associated with loss of hearing, there is relatively little information about the internal controls over aging within the auditory system. For example, what is the influence of long-term homeostatic regulation on cochlear integrity? What are the genetic factors associated with aging and hearing loss? Controlled systematic genetic recordkeeping in humans will be particularly useful in elucidating genetic controls of presbycusis.

Studies in homeostatic mechanisms of the inner ear, environmental effects on hearing, epidemiology of hearing loss, human genetics and otopathology will contribute greatly to understanding and preventing presbycusis. Specific research opportunities include:

- Epidemiologic studies.
- Studies of risk factors for apparent age-related hearing loss (diet, medications, heart disease, smoking or nonoccupational-noise exposure).
- Studies of potential treatment, such as regeneration of sensorineural components within the cochlea and drug replacement therapy for specific peripheral and central deficits due to aging.
- Studies directed at development and implementation of new signal processing strategies for auditory rehabilitation.

Animal models can be particularly helpful in clarifying the overlapping contributions of genetic predisposition, systemic disease and exposure to moderate noise levels in age-related hearing loss. These models can also identify different morphologic subtypes characterized by degeneration of hair cells and by structural changes in the stria vascularis (part of the inner-ear blood circulation), auditory nerve and brain. Interventions can also be studied in animal models. For example, does dietary change in animals with vascular disease reduce hearing loss while concomitantly reducing morbidity and mortality from involvement of other organ systems?

Clinical studies of presbycusis should attempt to delineate the separate effects of loss of sensitivity and aging on real-world speech recognition tests. To the extent that apparent central processing deficits are present, these deficits should be correlated with other measures of central nervous system structure and function such as magnetic resonance imaging, positron emission tomography and evoked potentials.

Blood and tissue should be analyzed as well as retained for future studies, and the study of temporal bone and brain tissue post mortem should be a continuing research priority.

Clinical intervention in presbycusis at present includes detection, measurement and rehabilitation principally through amplification with hearing aids. As presently practiced, these methods are effective, but their benefits in communicative skills and psychosocial well-being should be better documented. Methods of intervention can and should be improved. Better hearing aids are being developed, and their efficacy and acceptability with older persons will require specific attention. Early intervention, when hearing loss is milder, may improve later function as the loss progresses. New psychoacoustic and audiologic diagnostic methods may permit identification of patients who have a poor prognosis for successful use of hearing aids and lead to an appropriate modification of rehabilitative strategies.

Trauma and Environmental Effects

Detrimental influences from the environment have long been recognized as a major contributing factor to hearing loss in the general population. A number of factors have been identified. Others have been tentatively implicated. These factors can be classified into four broad categories:

- Exposure to noise, including steady, intermittent and impulse noise of various levels and durations. It may be associated with occupational activities (industrial plants, aircraft engines) or recreation (gunfire, rock music).
- Exposure to industrial by-products and pollutants such as the solvents toluene, xylene and styrene.
- Administration of clinically important and potentially lifesaving therapeutics such as aminoglycoside antibiotics, diuretics, antitumor agents (cisplatin) and salicylates (including aspirin).
- Results of trauma or accidents. These may be consequences of head injuries, intracranial surgery or barotrauma.

Depending on the type and severity of the insult, the resulting hearing loss may be partial or complete and reversible or permanent, or the disorder may manifest itself as tinnitus. In addition, hearing loss can be exacerbated by a combination of these insults or their interaction with other factors. A genetic predisposition for individual susceptibility may also exist.

While major inroads have been made in understanding the conditions under which these agents cause hearing loss, important questions remain unresolved. Moreover, the study of many of these problems still awaits the application of modern research techniques to elucidate the molecular mechanisms leading to the impairment of auditory function. Knowledge of these mechanisms will enable the design of rational approaches to prevention, amelioration and treatment, which are the major concerns in research on these auditory disorders.

Specifically, investigations are needed in epidemiology, pathogenesis and pathophysiology of hearing loss from environmental insults as well as into their prevention and management.

- For any suspected traumatic agent, the causal relationship to the observed hearing loss should be established.
- Electrophysiologic and histopathologic investigations may be helpful in determining the site of the insult within the auditory system.
- Investigations into the molecular mechanisms elicited by these insults and leading up to the hearing loss are fundamental to understanding, preventing and treating these forms of hearing loss. These studies require the entire repertoire of modern analytical techniques of biochemistry, pharmacology, physiology, electrophysiology and molecular and cellular biology.

In prevention and management, advances can be achieved through focus on the following strategies:

- Improved methods for screening hearing impairment in populations that are at risk (for example, certain industrial workers).
- Use of high-frequency audiometry for early detection of hearing impairment due to pharmacologic agents.
- Investigations into the predictability of permanent hearing loss, based on temporary shifts in hearing threshold.
- Determination of safe levels for occupational-noise exposure.
- Development and evaluation of more effective devices for ear protection and establishment of better methods for public awareness of this important health issue.
- Determination of the extent to which hearing impairment can be alleviated or reversed, based on early detection and removal of the insulting agents.
- Development of methods for protecting the inner ear from damage by drugs administered as pharmacologic agents. These methods, while preventing inner-ear damage, should not adversely affect the efficacy of the drugs.

- Investigations into the relationship between the structure of drugs and their ototoxicity. This research is directed to the design of new products or the modification of existing ones so that their ototoxicity is attenuated while their therapeutic efficacy is maintained.

- Development of procedures to test deleterious effects of drugs in models other than animals. Artificial membranes or cultures of sensory cells offer promising alternatives that should be developed further.

This multifaceted approach, ranging from the elucidation of molecular mechanisms through improved diagnostic and protective measures to pharmacologic prevention and new drug design, is essential. It has the potential of providing tangible benefits to the millions of Americans now at risk of environmental harm to their hearing.

The combination of noise exposure and organic solvents, which can be present in the workplace or as environmental pollutants, can potentiate hearing loss. A great deal of research is needed on the mechanisms of these interactions.

Research into the efficacy of possible therapeutic agents to reduce temporary or permanent hearing loss from noise exposure should be performed.

Experiments on the mechanisms of central and peripheral auditory injury resulting from various types of head or neck trauma should be carried out.

Acquired Sensorineural Hearing Loss in Infancy

Research is needed to study the susceptibility of the developing inner ear to such factors as maternal illness, substance use and abuse, and noise and trauma. The effects of the intrauterine environment require analysis. Studies should examine the individual differences in fetal susceptibility to hearing loss. The roles of prematurity, low birth weight and neonatal jaundice require continued investigation. Research is needed to study the effects of the environment of the newborn nursery, including the neonatal intensive care unit that admits newborns who are already at risk for hearing loss. The interaction of genetics, infections and various environmental factors in children born with a sensorineural hearing loss who subsequently develop a progressive and fluctuating hearing loss requires investigation.

Immune-Mediated Disorders

The immune system is crucial to the defense of the middle and inner ears against infection. In recent years, the role of immune mechanisms in many disorders of hearing has been recognized. Inflammation generated by the immune response undoubtedly contributes to tissue damage associated with infection. Evidence suggests that immune mechanisms induce hearing loss and are responsible for the progression of chronic otitis media. Immune mechanisms may also contribute to the pathogenesis of other disorders for which no cause has been established, such as Meniere's disease.

Research is needed on normal immune processes in the middle and inner ears as well as on the immune response to infecting microorganisms. Animal models of autoimmune sensorineural hearing loss should be developed, if possible, for research on the pathogenesis of this phenomenon. Application of research techniques of neuroimmunology to the auditory system should contribute to a rapid expansion of knowledge in this evolving field.

Problems exist in the diagnosis of autoimmune sensorineural hearing loss, and new diagnostic tests should be developed so patients with this treatable form of sensorineural deafness can be identified early in their course.

Multi-institutional controlled treatment protocols for autoimmune sensorineural hearing loss using corticosteroids, cytotoxic agents, plasmapheresis and related therapeutic modalities should be carried out.

Idiopathic Disorders

The middle and inner ear are subject to a variety of idiopathic processes, such as otosclerosis and perilymphatic fistula. Otosclerosis may have a genetic or viral cause, but more research is needed in determining the cause and effective medical treatment for otosclerosis. Perilymphatic fistula is a disorder which requires continued research into the cause, diagnosis and efficacy of treatment.

Meniere's Disease

Meniere's disease is an idiopathic disorder resulting in prostrating vertigo, fluctuating sensorineural hearing loss, tinnitus and the sensation of fullness of the ear. Diagnosis of Meniere's disease is difficult in patients in whom the disease is quiescent. New diagnostic methods utilizing electrocochleography, otoacoustic emissions and related tests should be developed.

The natural history of Meniere's disease should be thoroughly investigated. Studies are needed to determine the incidence of bilateral involvement. New animal models of Meniere's disease which more closely mimic the human disease should be developed. Genetic studies are needed to determine whether Meniere's disease has a hereditary basis. The effects of disruption of inner-ear homeostasis and fluid regulation of endolymph and perilymph by manipulation of hormonal and systemic factors should be thoroughly studied. A possible autoimmune basis for Meniere's disease should be thoroughly examined in humans and animals. The efficacy of medical or surgical treatment should be carefully studied with controlled clinical trials. The psychosocial effects of Meniere's disease should be studied. The consequences of untreated Meniere's disease should be elucidated.

Pathogenesis and Treatment of Tinnitus

Many persons with ear disorders hear noises (ringing, buzzing or roaring) when no external acoustic stimulus is present. This disorder is called tinnitus. At least 15 percent of the American population have frequent or constant tinnitus. Persons over 50 years of age are twice as likely to have tinnitus. Research on tinnitus is in its infancy and should be greatly expanded.

The natural history of tinnitus resulting from trauma or disease is incompletely defined. While some data on the prevalence of tinnitus in adult populations are available, the types and degrees of disability caused by tinnitus should be characterized and measured in population surveys.

Aspirin toxicity causes tinnitus, while simultaneously affecting inner-ear hair cell motility in a way that can be measured noninvasively. A possible relationship between otoacoustic emissions and some forms of tinnitus deserves additional study. The use of animal models can help elucidate mechanisms and sites of origin of tinnitus and test treatment such as acoustic masking and electrical suppression. These models should be developed because they promise new insights into tinnitus and normal inner-ear function.

Reliable and valid measures of tinnitus sensation and disability must be developed for use as outcome measures in studies of existing and new treatments.

Clinical Trials in Sensorineural Hearing Loss

For sensorineural hearing losses that are sudden, fluctuant or rapidly progressive, a variety of empirical therapies are currently used. Often these therapies are based on assumptions about the pathogenesis of the hearing loss. Fluctuating losses, for example, are often believed to be caused by endolymphatic hydrops and are treated with diuretics and salt restriction, while losses believed to be caused by inflammation or ischemia may be treated with corticosteroids or vasodilating agents, respectively. There is some evidence supporting the therapeutic efficacy of corticosteroids in certain patients with sudden hearing losses; in general, however, medical therapy for sensorineural hearing loss has not been shown to be efficacious.

There is a pressing need for properly controlled therapeutic trials in these areas. The use of agents affecting cochlear blood flow, for example, should be studied both in sudden and in rapidly progressive sensorineural hearing loss as well as in fluctuant hearing loss. The outcomes from various treatment strategies should be compared to the outcome of the natural history of the disease under study.

Some of the treatments now being used empirically may be effective only in certain subsets of patients. If better diagnostic tests were available for these patients, more rational and effective treatments could be readily determined. Further studies with animal models of sensorineural hearing loss are essential to provide insights into pathogenesis and to suggest to clinicians possible pathogenic factors in their patients.

Diagnostic Challenges

- The role of a viral infection in sensorineural hearing loss requires better diagnostic techniques.
- A diagnostic test for autoimmune hearing loss is urgently needed.
- A test to determine if the other ear of a person with Meniere's disease is at risk for development of the disease is needed.
- Diagnosis of perilymphatic fistula is difficult, and new objective diagnostic techniques are needed.
- Better diagnostic tools are needed to distinguish peripheral from central causes of hearing impairment, especially in patients with age-related hearing loss. The results should be validated with histopathologic studies of the peripheral and central auditory structures.
- Techniques for earlier identification of patients affected by neurofibromatosis type 2 are needed.
- Methods to identify patients at increased risk for noise-induced hearing loss and ototoxicity are needed.

Research Techniques

Although a variety of research techniques may be applicable, it is anticipated that epidemiology, molecular genetics, multicultural studies, and histopathology and pathophysiology of the damaged ear will be particularly useful in studying these hearing disorders.

Otopathology, particularly with newer techniques such as immunohistochemistry, three-dimensional reconstruction, electron microscopy and in situ hybridization, can be expected to add insights into the mechanisms of sensorineural hearing loss. The development of a national temporal bone pathology database will provide a valuable resource for studies of sensorineural hearing loss.

A national effort to collect and share cDNA libraries should be encouraged so that this technology can be applied to the study of causes of acquired sensorineural hearing loss. National registries and demographic studies will help provide much needed epidemiologic data on hearing loss of this nature.

Otitis Media, Otosclerosis and Other Middle-Ear Disorders

Otitis Media

Epidemiologic studies should be designed to reveal immune and genetic markers of otitis media-prone children. Study of environmental factors should identify prenatal, perinatal and postnatal conditions, as well as environmental pollutants, that affect the incidence of otitis media.

Anatomical, biochemical, neural, circulatory and developmental factors that affect the eustachian tube and middle-ear gas composition and pressure should be defined and correlated with the incidence, prevalence and pathogenesis of otitis media. Noninvasive tests of eustachian-tube function should be further developed.

The anatomic characteristics of the middle ear and related structures should be studied in various patient populations, including patients with asymptomatic middle-ear disease, employing the methods of systematic and quantitative human temporal bone pathology research. Methods of establishing cellular lineage and differentiation and investigating cellular regulatory mechanisms, including the molecular biology of secretory products in normal and pathologic conditions, should be emphasized in future research. The role of the round window membrane in possible inner-ear sequelae of otitis media should be a continued focus of research.

Microbiological, immunological and biochemical research opportunities include further elucidation of the mechanisms by which viral infections enhance or predispose to bacterial infections of the middle-ear space. Study of the role of bacterial-cell products in the inflammatory response and the genetic diversity and molecular features of bacteria involved in otitis media should be emphasized. Study of relevant adherence factors for each of the common middle-ear pathogens, characterization of genes encoding adherence factors and identification of the corresponding cell-surface receptors should be carried out to understand host and environmental factors that impact the microbial ecology in the nasopharynx. Future investigation should explore the role in homeostasis of secretion products and continue characterization of middle-ear inflammatory mediators.

Research to date has revealed important contributions of local and systemic immunity to middle-ear protection and inflammatory responses. Future research should determine the relative roles of systemic and local immune responses in the pathogenesis and mechanism of recovery from otitis media. This research may delineate the role of specific lymphocyte receptors and growth, proliferation and transcription factors in lymphocyte recruitment to and function in the middle ear.

High priority should be given to the development of vaccines that would reduce the incidence of viral and bacterial infections that cause otitis media and bacterial infections that cause meningitis. Priority should be given to further development and testing of pneumococcal capsular polysaccharide-protein conjugate vaccines for prevention of otitis media and meningitis. Protective mechanisms for nontypable *Haemophilus influenzae* and *Moraxella catarrhalis* should be further defined, and new genes for which expression products might be vaccine candidates should be identified.

Research should identify measures to detect otitis media and hearing loss in infants less than sixmonths of age, and improved methods of tympanometry and quantitative pneumotoscopy should be developed.

Study of treatments for otitis media should identify demographical, clinical, biochemical, microbiological and immunological factors that predict antimicrobial efficacy, complications and sequelae. Future research should emphasize antimicrobial and anti-inflammatory drug pharmacokinetic studies in the middle ear and safety profiles of existing and new antimicrobial and anti-inflammatory drugs. More effective pressure equalization of the tympanomastoid cavity should be a goal of therapeutic research. Multicenter, cooperative clinical trials should be explored to accelerate the testing of new treatment modalities on large, broadly representative population samples.

Since otitis media can have long-term effects on health and development, future research should measure the incidence of long-term otitis media sequelae including middle-ear and mastoid pathology and functional disability. These studies need to determine the effect of otitis media and hearing loss on speech, language, perceptual and cognitive development. Long-term sequelae of surgical and pharmacological interventions for otitis media are necessary including timing of antibiotic treatment. The pathogenesis and molecular and cellular mechanisms of the development of tympanosclerosis, chronic otitis media with and without perforation and cholesteatoma should be investigated further.

Otosclerosis and Other Middle-Ear Disorders

Understanding molecular and cellular mechanisms of otosclerosis should be a research priority. These mechanisms should include identification of specific viral antigens and identification of RNA or DNA in otosclerotic bone. Epidemiologic studies to search for genetic factors and preceding viral infections in otosclerotic patients should be performed.

The prevalence of perilymph fistulae should be determined, and tests for middle-ear perilymph should be developed.

Continuing studies of middle-ear micromechanics and development of middle-ear implant materials including ceramics, hydroxyapatite, plastics and banked middle-ear homografts should be pursued. Research should include determination of long-term results of middle-ear grafts and prostheses. Further study of the feasibility of partially or totally implantable electromechanical or electromagnetic drivers of the ossicular chain and temporal bone should be conducted. These studies should be done in light of increasing use of intense magnetic fields in medical diagnosis.

Assessment, Diagnosis, Treatment and Rehabilitation

The consequences of impaired hearing on speech perception are currently addressed by two approaches: prosthetic management and auditory rehabilitation. (Refer to the 1991 update of the Language and Language Impairments section of the National Strategic Research Plan for research opportunities involving the linguistic, educational and cultural concomitants of hearing impairment). Prosthetic management includes both the fitting of hearing aids, auditory prostheses and tactile aids, and in the case of children, the use of other technological aids to facilitate speech training and language development. Auditory rehabilitation attempts to remedy problems arising from hearing impairment by providing instruction in speechreading, communication therapy and training for children and adults who have difficulty with the interpretation of sound.

Assessment and diagnosis are prerequisites for treatment and remain essential components of rehabilitative management.

Assessment and Diagnosis

Quantum leaps have been made in the development and use of noninvasive diagnostic procedures to identify hearing impairment. An urgent research goal continues to be the early identification of hearing impairment in infants. The average age at which profound hearing impairment is first detected in this country is nearly three years, with less severe losses detected even later. Detection of hearing impairment during late stages of language development has a negative impact on the acquisition of communicative, academic and social skills in children. There are powerful strategies for early identification of hearing impairment in newborns and infants. Research is needed to study these strategies to determine their effectiveness in screening for hearing impairment and to determine the best method for implementation in various settings.

Advances in technology hold promise for the development of improved assessment and diagnostic procedures for adults, as well as for infants and children. Research opportunities in the area of assessment and diagnosis include:

- Establishment of validity, reliability and efficiency of new and existing audiologic test procedures.
- Application of new and emerging information about normal and pathological processes to improve diagnostic and evaluative techniques.
- Application of new and emerging technologies to improve diagnostic and evaluative techniques.

Treatment and Rehabilitation

Prosthetic Management

Fundamental Understanding

While much remains to be learned about the characteristics of normal auditory function, a major lack of knowledge exists in the current understanding of how impaired auditory systems encode the cues salient for communication, of how auditory perceptions are distorted by hearing impairment and of the mechanisms of the ear and central auditory system that underlie these changes. Such an understanding is basic to the development of prosthetic devices and rehabilitative strategies.

This area of research should include physiologic and perceptual studies of impaired auditory function, including the effects of aging and electrical stimulation; studies of speech perception by hearing-impaired persons; studies of the linguistic, social, emotional and vocational consequences of hearing impairment; and studies of nonauditory processing disorders associated with hearing impairment.

Hearing Aids

Continued research on hearing aids is important and timely. The population who can benefit from hearing aids is likely to grow as the population ages. In addition, progress in the miniaturization of electronic devices and transducers as well as the technology of digital signal processing may far outstrip the basic understanding required to apply these advances successfully. Specific research opportunities include:

- Research on the design and optimization of hearing aids consistent with emerging knowledge of impaired auditory function.
- Application of promising technologies and concepts to the design of improved hearing aids, including increased directionality and noise suppression, higher functional gain and output levels, reduced acoustic feedback, adaptation to variation in input level and improved signal processing in reverberation. The potential for functional benefits associated with implanted hearing aids that drive inner-ear structures directly should be investigated.

- Development of improved techniques for the fitting, selection and validation of hearing aids for both children and adults.
- Refinement of the theoretical basis, including standardized materials and methods, for evaluating hearing aid efficacy.
- Evaluation of the efficacy of new and existing hearing aids, so that appropriate devices can be recommended to impaired listeners.
- Evaluation of the efficacy of new hearing aid technology for specific subpopulations of individuals with hearing impairments, based on age, etiology, degree of hearing impairment and site of lesion (sensory versus neural versus central).

Neural Prostheses

Implantable neural prostheses are increasingly used to treat profound sensorineural hearing impairment. One type of prosthesis is placed directly in the cochlea; another is introduced within the auditory pathway of the central nervous system.

The peripherally placed cochlear implant has become an accepted prosthesis for both adults and children. More than 80 percent of adult recipients of cochlear implants receive substantial benefit in communication when speechreading is possible and about one-half of these individuals are able to understand some speech without speechreading. Of those people who can understand speech without speechreading, about one-half are able to communicate by telephone. Substantial benefits have also been observed for children, including those deafened prelingually; moreover, there is evidence that the benefits derived improve with continued use of the prosthesis. New sound processing schemes based on high-rate, pulsatile stimulation have been shown to provide even greater levels of speech perception.

Improved prostheses suitable for placement within the central auditory pathways have been developed. Initial studies of selected patients with auditory brain stem implants have produced encouraging levels of speech segment and word reception, and the potential of this approach for aiding deaf persons is great. Future refinement of this approach should be pursued using strategies in which basic research results (e.g., on the tonotopic organization of central structures) are interfaced with technical and clinical research on electrode design and coding strategies.

Research on neural prostheses, in addition to providing amelioration of hearing impairment, provides an important opportunity for examining auditory function as well as for studying maturation and plasticity within the auditory system. Research opportunities in neural prostheses include:

- Developing improved speech coding schemes capable of providing enhanced perception to more implant recipients.
- Understanding the factors that determine the degree of benefit provided to a specific patient by a specific prosthesis and thereby facilitating the prediction of the potential for success before implantation.
- Developing longitudinal studies of the development of auditory, speech perception and production and language skills in hearing-impaired children fitted with cochlear implants, hearing aids or tactile aids.
- Investigating the potential role of nerve growth factor and other growth factors in stimulating the regrowth and the maintenance of nerve terminals in the cochlea.
- Studying the role of electrical stimulation in prolonging the survival of neural elements.
- Developing improved electrode systems that will allow for a greater number of perceptual channels and increased channel selectivity, yet will be suitable for replacement as required.
- Developing and studying electrode systems and coding techniques appropriate for central auditory system prostheses.
- Developing and validating models of the factors that affect electric-current spread in auditory structures.
- Developing models of the ways in which electrical stimuli elicit distributed patterns of neural activity at various levels in the auditory system to achieve a full understanding of prosthetic function.

Tactile Aids

Studies of natural methods of tactual communication employed by the deaf and blind (e.g., the Tadoma method of speechreading and the tactile reception of sign language and finger spelling) provide evidence that the skin and proprioception can serve as useful communication channels. Thus, there is strong evidence that successful prosthetic devices can be developed based on coding acoustic signals for the tactile and kinesthetic senses. Several multichannel tactile aids have been developed and are currently being used by deaf people.

- Coding techniques capable of extracting the necessary information-bearing cues from the acoustic speech signal and encoding the required tactile sensations should be developed.
- The efficacy of existing tactile aids, particularly in children after

extended periods of use, should be studied.

Supplements for Speechreading

Recent advances in speech processing and automatic speech recognition technologies may provide substantial benefits to hearing-impaired individuals who rely on speechreading for communication. The visual signal is impoverished so that, for example, distinctions between consonants based on voicing are not easily made. When the resulting confusions are resolved, as in the case of manually cued speech, near normal communication is possible using vision alone. Even simple auditory and tactile signals can improve speechreading substantially. Recent research greatly increases our understanding of the benefits to be expected from these supplements and may permit analysis in clinically useful terms.

- Additional research on auditory supplements is required to establish how to select and match the supplementary signal to the characteristics of the impaired auditory system.

- The application of speech recognition technology to the automatic generation of cued speech also warrants study. Research is needed to develop recognition and display techniques appropriate for speechreading supplementation and also to establish the levels of performance that must be achieved if useful benefits are to be provided.

Telecommunication Devices

Research is needed to develop and evaluate visual technologies for hearing-impaired individuals such as visual telephone communication, electronic mail, video conferencing, Videotex and real-time captioning. Application of these technologies has important implications for maximizing rehabilitative opportunities for individuals with hearing impairment.

Auditory Rehabilitation

Adults and children with acquired sensorineural hearing loss require rehabilitative intervention, including opportunities to adjust to diminished hearing, to adapt to sensory prostheses and to develop improved speech perception skills in visual, auditory and auditory-visual modes. Much of the applied work in this area has developed with minimal guidance from research. The establishment of a scientific basis for continuation and expansion of this work is a high priority. Specific research opportunities include:

- Establishment of the prerequisites and essential components of effective rehabilitation.

- Establishment of appropriate and realistic expectations for the outcome of rehabilitative strategies.

- **Establishment of the need for and efficacy of rehabilitative intervention in various populations with acquired sensorineural hearing loss.**

Summary of Research Recommendations

Research Opportunities in Hearing

Transduction and Homeostasis

- **Measure the mechanical changes in hair bundles during transduction and adaptation and determine how these mechanical changes affect basilar-membrane motion.**
- **Elucidate the mechanism of outer-hair-cell motility and investigate the role of this process in frequency tuning on the basilar membrane.**
- **Relate the unique structure of the hair cell's afferent synapse to its role in sensitive, high-frequency synaptic transmission and identify the hair cell's neurotransmitter and its postsynaptic receptor and signaling mechanisms.**
- **Identify and characterize the molecular substrates underlying transduction, motility and cellular homeostasis.**
- **Examine the homeostatic processes that regulate the cochlear environment, including the control of blood flow, ionic balance and intercellular communication.**
- **Construct cDNA libraries representing messages for proteins involved in transduction, motility and ionic regulation; probe the libraries in an effort to identify and sequence the proteins that are the transduction channel, the adaptation motor, the afferent transmitter receptor and growth-factor receptors.**

Sound Processing in the Brain

- **Study the functional connections of neurons and synaptic mechanisms at all levels of the auditory system.**
- **Relate neurophysiologic descriptions of the auditory system to animal and human psychophysical data.**
- **Characterize fully the afferent and efferent auditory systems.**
- **Study the potential for central reorganization subsequent to peripheral or central injury, determining the plasticity of the mature auditory system and the impact of modified auditory input upon its organization.**

- Develop models to provide concise descriptions of normal and abnormal auditory function.

Auditory Perception

- Define the relations between complex acoustical signals and the resulting perceptual experiences of listeners.
- Elucidate the perceptual correlates of sound coding in the auditory nervous system.
- Enhance the understanding of sound location in animals and humans.
- Relate emerging knowledge about perceptual organization to the development of a comprehensive model for auditory perception of spoken language.
- Extend research conducted on listeners with normal hearing to study the consequences of sensorineural hearing loss on the perception of complex sounds and spoken language.

Development, Aging and Regeneration

- Assess the normal life cycle of the auditory system, including the definition of critical periods for the development of auditory processes.
- Evaluate the limits of neural plasticity in the auditory system.
- Define the influences of environmental, nutritional and pathologic factors that compromise the normal life cycle of the auditory system.
- Study the embryonic mechanisms for the formation of the normal ear and characterize the mechanisms underlying normal cell proliferation and differentiation.
- Study the developmental course of complex sound and speech perception in infants and young children.
- Elucidate the many aspects of age-related hearing loss in animals and humans.
- Isolate and identify molecular events that evoke proliferation leading to the replacement of lost sensory cells.
- Assess the roles of known and suspected growth factors that may influence the production and development of replacement sensory cells and the formation and maintenance of their contacts with neurons.
- Explore the molecular, morphologic, physiologic and behavioral consequences of sensory cell regeneration.
- Identify the mechanisms that determine neuronal survival and

explore paradigms that may protect and maintain auditory neurons after trauma or deprivation.

- Characterize the morphogenetic processes of the embryonic ear.
- Identify the intercellular signals that regulate developmental specialization of cells that perform the sensory and supporting functions of the cochlea.
- Determine which growth factors mediate the trophic interdependence of sensory cells and neurons in the auditory system and assess the strength and the timing of those interactions in normal development and during regeneration.
- Investigate the potential for sensory cell replacement and regeneration in mammals.
- Study the role of electrical stimulation in prolonging neuronal survival.

Research Opportunities in Hearing Impairment

Hereditary Hearing Impairment

- Map, isolate, clone, sequence and characterize genes responsible for hearing impairment in humans and animals.
- Solicit the participation of families in studies of hereditary hearing impairment. Educate professionals serving people with hearing impairment regarding selection criteria for these families.
- Develop clinical and physiological tests which identify carriers of recessive hearing loss genes.
- Develop comprehensive inner ear-specific cDNA libraries from humans and laboratory animals.

Acquired Sensorineural Hearing Loss

- Study the incidence, pathophysiology and treatment of hearing loss and ear disease associated with human immunodeficiency virus and the opportunistic infections it causes.
- Study the incidence, pathophysiology, diagnosis and treatment of hearing loss associated with viral and bacterial infections.
- Study the natural history, biology, treatment and rehabilitation following treatment of neoplasms which affect the temporal bone.
- Study the effects of trauma, environmental factors and ototoxic drugs on hearing; new means of establishing the causal relationship of the hearing impairment to the traumatic event or injurious agent; improved screening techniques for

prevention; location of the insult within the auditory system; and identification of the molecular mechanisms underlying this damage so that strategies for treatment can be developed.

- Study the possible causes of acquired sensorineural hearing loss of infancy to establish precise causes so that preventative interventions can be developed.
- Study the normal immune host responses involved in diseases of the middle and inner ears.
- Establish and investigate animal models of autoimmune sensorineural hearing loss, determine the inner-ear targets of autoimmunity, develop specific and sensitive diagnostic tests for this condition in humans and conduct controlled treatment trials to determine safe and effective therapeutic intervention.
- Study the idiopathic forms of hearing loss, such as otosclerosis and perilymphatic fistula, with attention toward establishing a cause, improving diagnosis and determining efficacy of treatment.
- Determine the natural history, pathogenesis and treatment of tinnitus.
- Perform clinical trials to determine the most efficacious treatments for the various causes of sensorineural hearing losses.
- Study the natural history, epidemiology, diagnosis, pathogenesis and treatment of Meniere's disease.
- Establish more sensitive diagnostic tests for viral deafness, separation of peripheral from central causes of hearing loss, neurofibromatosis type 2 and those at increased risk for noise-induced hearing loss and ototoxicity.
- Apply newer research techniques involving molecular biology, immunohistochemistry, electron microscopy and computer-assisted reconstruction to the study of the temporal bone.
- Establish a national consortium to create cDNA libraries of the inner ear so that this technology can be made available to investigators in the field.
- Develop national registries to collect epidemiologic data on hearing impairment as well as diseases which affect the ear.

Otitis Media, Otosclerosis and Other Middle-Ear Disorders

- Study the epidemiology and incidence of otitis media among multicultural populations with attention to environmental versus genetic factors.

- Study the anatomy, biochemistry and development of the eustachian tube and its role in otitis media and maintenance of middle-ear gas composition.
- Study the cellular elements and their function in the middle ear.
- Study the microbiology, immunology and biochemistry of the middle-ear inflammatory response.
- Study the role of local and systemic immune responses in the pathogenesis and recovery from otitis media.
- Develop vaccines for the prevention of otitis media and meningitis.
- Develop diagnostic measures for otitis media in infants under six months of age.
- Study existing and new treatment modalities for otitis media to establish their efficacy and safety.
- Study the long-term sequelae of otitis media on middle- and inner-ear function, middle-ear and mastoid pathology and speech, language, perceptual and cognitive development.
- Study the epidemiology and the molecular and cellular mechanisms involved in the pathogenesis of otosclerosis.
- Develop a precise diagnostic test or assay for perilymphatic fistula.
- Study the micromechanics of the conductive hearing apparatus and develop improved middle-ear implants and electromechanical or electromagnetic drivers of the ossicular chain.

Assessment, Diagnosis, Treatment and Rehabilitation

- Develop and validate new procedures to identify hearing loss and evaluate the perceptual consequences of hearing loss.
- Develop and evaluate new techniques for effective auditory rehabilitation of children and adults with hearing impairment.
- Continue the development and evaluation of sensory aids for persons with hearing impairment including hearing aids, cochlear implants, auditory brain stem implants, tactile aids and speechreading supplements.
- Continue the development and evaluation of visual technologies for individuals with hearing impairment.

BALANCE AND THE VESTIBULAR SYSTEM

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BALANCE AND THE VESTIBULAR SYSTEM

Overview

The vestibular system maintains our balance and posture, regulates locomotion and other volitional movements and provides a conscious awareness of orientation in space and a visual fixation in motion. Disease, aging, exposure to unusual motion or altered gravitational environments (e.g., aerospace flight) can impair balance. In the United States, approximately two million adults have chronic impairment from dizziness or a balance problem. For example, there are an estimated 38,000 new cases of Meniere's disease each year, one of many disorders that affects the vestibular system, and dizziness is the most common reason for seeking medical care in the over-75-year age group. A major consequence of vestibular disturbance is diminished capability and desire for purposeful activity. There may also be incapacitating effects on motor task performance and sensorimotor integration. Furthermore, motivation, concentration, memory, food intake and digestion and many other human activities may be adversely affected.

The vestibular receptors located in the labyrinth of the inner ear signal motion and position of the head. Nerve fibers connecting these receptors to the brain provide information about head movements to produce vestibular reflexes. Brain circuits integrate vestibular information with other sensory signals from the eyes, skin, muscles and joints to produce a complex set of reflexes that interact to maintain posture and visual fixation in motion. In addition, the signals contribute to an internal representation or picture of body orientation and self motion.

The vestibular system is a complex, highly interactive set of brain mechanisms capable of continuous adaptations to changes in the body and the environment. Because it has many components, there are many symptoms that indicate its malfunction, which range from mild discomfort to total incapacitation. Although balance is normally an automatic, unconscious process, it is essential for purposeful movement and effective communication.

Understanding how the vestibular system works is a scientific and technical challenge. The fluid-filled receptor end-organs that detect motion and head position are encased in bone and are difficult to access, manipulate and study. The system is complex because it integrates many kinds of sensory information and utilizes a variety of neurochemical transmitters, and its malfunction results in a multitude of symptoms. The complexity of vestibular system function requires an interdisciplinary approach, including rigorous anatomical, physiological, biochemical, molecular biological, pharmacological, behavioral, perceptual and clinical studies. Biological data should be incorporated into mathematical computational models to examine and understand the integrated action of vestibular receptors and brain circuits in maintaining balance, orientation and the visual fixation and postural stability required for locomotion and other volitional movements. The resulting models should be utilized to predict changes that will result from pathologic conditions. Symptoms of these conditions should be evaluated in the context of the model predictions to reach a global understanding of the normal vestibular system and its pathophysiology.

Symptoms

The symptoms of vestibular system dysfunction are varied, reflecting the complexity of functional interconnections of the vestibular system with vision, tendon and joint position sensors, the digestive system and even the psyche (anxiety disorders).

Dysfunction of the vestibular system, particularly the inner ear and its interconnections with the brain, may cause hallucination of movement, variably described with such terms as dizziness, disorientation, vertigo, spinning, floating, rocking, lightheadedness, giddiness, sense of falling, imbalance, unsteadiness, or difficulty walking.

Symptom characteristics and the degree to which the patient is incapacitated depend upon the nature of the disorder. The symptoms may be episodic or continuous and may vary in frequency, severity and rapidity of onset. If there is damage to the system, the location (either in the inner ear or brain) as well as the magnitude of that damage play roles in the generation of symptoms.

Balance system dysfunction, if severe enough, can also provoke responses in the digestive system (nausea, vomiting and diarrhea), circulatory system (pallor, changes in blood pressure and pulse) and skin (perspiration, cold or clammy sensation).

The psychological impact of vestibular symptoms should not be underestimated. The fear of falling, with the chance of physical injury, adversely affects the individual's sense of independence and quality of life, particularly in the elderly. Similarly, the fear of a sudden attack of dizziness with socially embarrassing ataxia, nausea and vomiting can cause individuals to become withdrawn. Subconscious fear may play a role in agoraphobia and subtle dysfunction of the vestibular system may underlie difficulties in handwriting and reading. Vestibular dysfunction adversely affects the ability to perform the most routine activities, such as taking a shower, housekeeping duties and driving an automobile, and may prevent patients from holding high-risk jobs, e.g., telephone line-man, mechanic and bus driver.

Disorientation, i.e., wrongly perceived tilt or motion of the body relative to the environment, can arise from abnormalities in the vestibular system or result from subjecting the normal vestibular system to an abnormal environment.

Motion sickness is currently regarded as the brain's response to conflicting sensory messages about the body's orientation and state of motion. The sensors involved include the vestibular part of the inner ear, the eyes and body pressure and joint position sensors. Nausea, vomiting and poor concentration are symptoms provoked by "sensory mismatch."

Dizziness comprises a spectrum of disorders ranging from lightheadedness and giddiness to frank vertigo and dysequilibrium. Attempts to determine precisely the true incidence of vertigo/imbalance stemming from peripheral and central vestibular system dysfunction are foiled by the nature of the disorders and the complexity of the balance control mechanisms. However, it is clear that balance disorders afflict a large proportion of the population, particularly the elderly.

Prevalence and Costs

Recent estimates exist for the prevalence of balance disorders in general, Meniere's disease and benign paroxysmal positional vertigo (BPPV). Examination of hospital statistics by discharge diagnosis shows that for those people under 65 years of age, 185,680 hospital days per year, on average, are provoked by dysequilibrium. In the general population (all ages), 347,000 hospital days are incurred because of "vertiginous syndromes," 202,000 because of "labyrinthitis" and 184,000 because of "labyrinthitis unspecified," with several thousands more accounted for by other balance disorders, e.g., Meniere's disease. The diagnosis of dizziness or dysequilibrium accounted for 221,000 of the primary discharge diagnoses in 1983. In the 45-to-64-year-old group, 1.3 percent of all visits to internists are related to vertigo or dizziness, affecting a relatively similar percentage of men and women.

Meniere's disease affects 15.3/100,000 individuals per year, resulting in about 38,250 new cases per year in the United States; in contrast, an incidence of 46/100,000 was found in a Scandinavian population, which would translate into 115,000 new cases per year in the United States. The prevalence figures are even more striking with a rate of 218.2/100,000. It is estimated there are 545,000 individuals in the United States with Meniere's disease.

In Japan, BPPV was determined to affect 10.7/100,000 individuals, with a great deal of inter-regional variability. The Japanese study determined that BPPV peaked in incidence in the fifth decade for both men and women, but that women were more commonly affected than men. BPPV occurred about two-thirds as frequently as Meniere's disease. The incidence of Meniere's disease in Japan is 16.0/100,000, very close to the incidence in the United States.

In looking at outpatient visits, 2.9 percent of visits to internists by the over-65-years-old group are because of dizziness or vertigo; in the over-75-years-old group, 3.8 percent of visits were for dizziness or vertigo, the number one reason for going to the physician. Seven percent of those in the over-85-years-old group present to the doctor because of dizziness or vertigo. These numbers reflect just the tip of the iceberg: an interview of those elderly at home showed 47 percent of the men and 60 percent of the women over the age of 70 complained of dizziness or vertigo.

In 1976, an estimated $500 million was expended just on visits to physicians for dizziness or vertigo. Assuming, conservatively, a five percent rate of inflation, the costs for medical care alone will approximate one billion dollars in 1991. To this figure must be added the cost of diagnostic testing, as well as therapy. The cost of falls, which potentially lead to fractured limbs, hospitalization, surgery, pneumonia and even death, must also be factored in. An estimated 15 to 23 percent of those over the age of 65 years who fall fall because of dizziness or vertigo.

The psychological toll of balance disorders on their victims is considerable; of those over the age of 65 years, at least 34 percent believe that dizziness keeps them from doing things they otherwise could do. This is not a happy way to spend one's "golden years."

If one considers military costs, the Army, Navy and the Air Force lose an average of 30 pilots and their aircraft every year to pilot disorientation and subsequent error. This loss of materiel conservatively represents an estimated cost of $300 million per year. In times of strife, cost estimates are increased three- to four-fold. Also, two-thirds of all astronauts experience motion sickness that can severely reduce their effectiveness for the first three days into orbital flight.

Diagnosis and Treatment

Evaluation of vestibular function has improved in the last 15 years due to the development of tests based on modern anatomic and physiologic concepts and the application of technical advancements. For example, studies of individual neurons are providing data upon which models have been developed to understand precisely vestibular, visual and somatosensory inputs involved in gaze stabilization, balance and orientation. Technical advancements in computer hardware have enabled clinicians to control angular and linear acceleration devices. Methods are being developed to measure different reflex functions (e.g., movements of the eyes, body or extremities) with the aid of microcomputers and programs that permit automatic analysis of data with accuracy and ease.

Tests cannot be limited to measurements of only one aspect of the balance system, however. Normal vestibular and balance function is a result of information about head movement and position from the inner ear, visuo-spatial relationships from the visual system and body relationships to the environment from the somatosensory system. Current methods of evaluating patients with vestibular disorders consist of a battery of tests that quantify the vestibulo-ocular reflex (VOR), the visual-oculomotor system and postural responses.

Better techniques to quantify vestibular function and its interaction with other systems, in addition to techniques that aid in early diagnosis such as magnetic resonance imaging (MRI) and techniques that permit evaluation of blood flow and metabolic function of the brain, are resulting in improved diagnosis and management of patients with vestibular disorders. Advancements in our understanding of the pathophysiology of vestibular disorders have also contributed to better medical and surgical management. For example, mortality following resection of vestibular tumors has decreased from 50 percent to less than one percent.

Rehabilitation procedures are being developed that provide an additional approach to treatment for vestibular disorders. Specific vestibular exercise programs facilitate the rate and final level of recovery from vestibular disorders.

A Current View of Vestibular Function

Understanding the Molecular, Cellular and Neural Basis of Peripheral and Central Vestibular Function

Many of the vestibular reflexes serve to stabilize and coordinate movements of the eyes, head and body. These processes are collectively referred to as the vestibular reflex systems.

The vestibular receptor organs transduce the forces associated with head accelerations and changes in head position relative to gravity. The result is excitation of the nerves leading to control centers in the brain, which use these signals to develop a sense of orientation and to activate automatically muscles that subserve movements of the eyes, locomotion and posture.

While the basic receptors and neural structures are genetically determined, the development and fine-tuning of vestibular function is a dynamic process that is dependent upon use and interaction with the environment throughout life. There must be an ongoing process of calibrating reflexes in order to adapt to physical changes in the musculoskeletal system during growth and development as well as to compensate for disorders (for example, inner-ear disease or visual loss) and to adapt to changes in the environment (such as an altered gravitational field, as in space). Thus, the proper responses to vestibular information require learning and memory.

Signal Transduction by Vestibular End-Organs

There are five vestibular end-organs. Two of these, the utricular and saccular maculae, transduce linear acceleration forces acting on the head, while the other three, the cristae of the semicircular canals, transduce angular acceleration forces. The five organs are so arranged in the temporal bone that they collectively provide the brain with a three-dimensional reconstruction of the position and motion of the head relative to the Earth.

Each end-organ consists of a sensory epithelium composed of sensory hair cells and supporting cells, innervated by afferent nerve fibers from the vestibular nerve. Hair cells contain ciliary bundles (hairs) that protrude from their apical surfaces and are embedded in gelatinous structures, the otoconial membranes of the maculae and the cupulae of the cristae. These structures couple the forces acting on the head to the cilia resulting in bending of the cilia. Displacement of the ciliary bundles regulates the opening of transduction channels, thought to be located near the ciliary tips. When the channels are opened, an electrical transducer current flows into the hair cell and changes the voltage. The transducer current modulates ionic currents flowing through the basolateral surface of the hair cell. The basolateral currents alter the electrical response of the hair cell. In addition, one of the basolateral currents adjusts the intracellular concentration of calcium ions and thereby regulates the release of as yet unknown chemical neurotransmitters from the hair cell to the afferent fibers contacting (synapsing with) the hair cell. The result is a change in the nerve impulse frequency of the afferent fibers. Even at rest, hair cells continue to release neurotransmitters and thereby cause nerve fibers to have a background or spontaneous activity. Bending the cilia in one direction causes an increase in transmitter release and nerve activity; bending in the opposite direction results in a decrease. In addition to their afferent innervation, the receptor organs are also provided with efferent nerve fibers arising from the brain and contacting hair cells and afferent terminals. By means of this efferent innervation, the brain can regulate ongoing sensory processing by the end-organs, as well as modulate their function on a longer time scale.

The afferent nerve fibers transmit their impulse activity to the vestibular nuclei and to the cerebellum. These structures are extensively interconnected with each other and with other centers in the brain stem and spinal cord that modulate the activity of the muscles of the eyes, head and body.

Reflex Control of Posture and Gaze

Afferent fibers from the semicircular canals and the otolith organs synapse with neurons in the vestibular nuclei of the brain stem, which form the starting point of neural circuits that regulate movements of the eyes, head and body. These movements take the form of reflexes that compensate for perturbations of head or body position.

Postural reflexes result from the integration of vestibular signals with input from visual and somatosensory receptors and other motor-control systems and generate patterns of activation of leg, trunk and neck muscles that stabilize posture and prevent falling. Maintenance of posture depends on the generation of different stabilizing movements depending upon the context in which adjustments must occur. Vestibular contributions to postural control are difficult to isolate from other postural stabilizing responses.

The direction of visual regard is regulated by gaze reflexes, which are better understood than postural reflexes. Such regulation is required to maintain stability of images on the retina, without which visual acuity is severely reduced. One such reflex, the vestibulo-ocular reflex (VOR), causes eye movement equal but opposite to head movement. When the head is rotated to the right, the horizontal semicircular canal in the right ear is activated and that in the left ear inhibited. Reflex circuits transform these changes in canal afferent activity into activation of muscles that move the eyes to the left by the same angle as the head movement so that the eyes remain directed to a fixed point in space as the head moves. In analogous fashion, when the head is displaced linearly upward (e.g. during running), saccular otoliths are stimulated; and by way of reflex pathways projecting to the ocular motor nuclei, the eyes are moved downwards to compensate for the head displacement.

Despite its seeming simplicity, the VOR requires complex and very accurate processing of semicircular canal, visual and otolith signals to generate the required compensatory eye movement. The angular acceleration signal provided by canals must be converted into a change in angular position of the eyes. Because the canals are not exactly aligned with eye muscles, signals from all canals must be combined to produce a spatial transformation from the three-dimensional coordinate frame of the canals to that of the eye muscles. These problems become even more complex in the vestibulo-collic reflex, which must control over 30 neck muscles to stabilize the biomechanically complex head-neck system. Remarkably, the brain is able to perform these functions with relatively simple reflex circuits. The key is in having a parallel processing system with a multiplicity of neurons at each stage of the circuit, which gives the system great processing power and flexibility. Such systems can best be understood by computerized modeling techniques that can represent and explore their structure and computational capabilities.

The most direct neural circuits involved in gaze reflexes are three-neuron vestibulo-ocular and vestibulo-collic reflex arcs that interconnect vestibular afferent fibers, relay neurons in the vestibular nuclei and motor neurons that control eye or neck muscles. Each connection between a labyrinthine receptor and a pool of motor neurons involves several classes of relay neurons, each of which collects input from a different set of vestibular and visual or somatosensory receptors and projects to either a few related or many diverse motor pools. These classes of relay neurons may have distinct biophysical and pharmacological properties which allow them to be regulated independently and which may permit discrete therapeutic intervention to restore deficient reflex function once the mechanisms are known. In addition, the brain has a repertoire of more complex processes for regulating gaze which involve predictive switching, like that seen in postural systems. These are implemented by more complex neural circuits and are as yet poorly understood.

Not surprisingly, to remain effective for visual stabilization, VORs must interact with the visual world during head movements. By receiving visual feedback during head movements, VORs may update their response properties to match what is required to maintain visual stability at any particular time and under a variety of circumstances. That is, the VORs exhibit adaptive plasticity. In addition, recent evidence has shown that VOR characteristics are affected by the vergence state and the direction of gaze in space, indicating that the VOR is not an isolated, simple reflex, but has response properties which are determined by integration of inputs from a variety of nervous system mechanisms and sensors other than vestibular ones.

Sensory Integration in Spatial Orientation, Perception and Motion Sickness

Spatial orientation is the relationship of the head and body to the Earth and to the Earth's gravity. The vestibular system and weight sensors provide information about how the body is oriented relative to the Earth, while other senses such as vision define the relationship of elements of the environment to the body. Balance and equilibrium are processes by which persons move and maintain head and body posture. Maintaining orientation and balance requires the integration of information from many sources, especially the ears, eyes, skin, muscles and joints, and the transformation of these signals into coordinated patterns of muscle activity. To maintain balance and equilibrium under a variety of sensory and support surface conditions, combinations of sensory signals and muscle activity patterns must be interpreted appropriately.

Many sensory inputs are required for the production of a coordinated perception of head and body movement in space. The visual system tells the vestibular nuclei whether the reflexes produced by activation of vestibular end-organs provide the amount of gaze compensation that is required. Visual feedback is critical for proper operation of the VOR. This involves portions of the vestibulo-cerebellum, which play a role in adjusting the VOR when visual feedback indicates that it is not correctly stabilizing gaze. Disease of the cerebellum can result in faulty VOR calibration, poor gaze compensation during movement and imbalance and disorientation. Because vestibular signals interact with all of the major sensory systems, a large number of disease processes can impair balance and orientation. While it is clear that many brain structures are involved in determining orientation and balance, their precise roles remain to be determined.

The vestibular system operates largely automatically and without conscious awareness. When normal coordination among the senses is disrupted by disease, a disturbing symptom, known as vertigo, occurs. Similarly, passive or unusual motion conditions (car and air travel, sea voyages and space flight) induce motion sickness, probably due to unusual combinations of signals from various sensors of motion. Mechanisms underlying the symptoms associated with vertigo and motion sickness are not well understood and are major unsolved problems as exemplified by the very high incidence of motion sickness which occurs during pilot training and reports that about two-thirds of the astronauts suffer from space motion sickness.

Gaze mechanisms involve not only eye movements but head movements as well. Frequently vestibular lesions that affect balance and orientation also affect the way the head is moved. This effect can lead to inappropriate stabilization of the head in an attempt to avoid unpleasant dizziness or vertigo, as well as possible dysfunction of the neck muscles and joints, which can also cause a sense of imbalance. Relatively little is known about the clinical effects of vestibular lesions on neck muscle and joint action or the reverse.

Adaptive Changes in Vestibular Function

A remarkable feature of the vestibular system is its potential for adaptive change (plasticity). This adaptive capacity allows the system to compensate for changes that occur during development and aging or as a result of lesions. Most striking is the rebalancing of the system that occurs after loss of one vestibular nerve or labyrinth. The large postural imbalance and uncontrollable drift of the eyes that are seen immediately after a lesion disappear nearly completely over the course of a few weeks, although these signs can return if the system is stressed. To accomplish this recovery, the adaptive system must compensate for the loss of a large amount of ongoing neural activity that would normally come into the vestibular nuclei via the lesioned nerve. Experimental studies are beginning to reveal some of the neural and pharmacologic aspects of the multifactorial process that is involved.

Another example of adaptive vestibular control is the plasticity of the VOR, which is experienced by anyone who is fitted with a new set of prescription spectacles. Because the lenses magnify or reduce the size of the visual scene, images appear unstable when the head is moved: the VOR is still compensating for image motion that would be different without the lenses. This instability resolves in a few hours because the adaptive system changes the "gain" of the VOR and thus adjusts the speed of reflex eye movement appropriately for the new lens system. Experimentally, large changes in gain can be induced by having subjects wear magnifying and reducing lenses and even the direction of the VOR can be altered by appropriate pairing of head and image motion. Thus, in addition to its clinical relevance, this VOR plasticity has become an important model system for understanding the neural basis of motor learning.

The role of the cerebellum in this process is the subject of current controversy. Cerebellar lesions abolish VOR plasticity, but one group of investigators believe that the cerebellum merely generates error signals that induce learning in the brain stem while another group has provided evidence that cerebellar circuits themselves can undergo plastic changes which account for VOR plasticity. This healthy controversy places the vestibular system at the forefront of attempts to understand sensorimotor systems. What is learned about the role of the cerebellum in the VOR will help scientists understand its role in regulating other types of movements.

As humans venture into space, they will be exposed for increasing periods of time to gravito-inertial fields different from those of Earth. Exposure to microgravity results in profound changes in the balance system. Extended exposure might be expected to have consequences on otolith reflexes involved with control of eye and head movements, posture and locomotion since those reflexes have evolved and function in the gravity of Earth. For example, the linear VOR, which depends on accurate information from otoliths, as well as reflexes dependent upon canal/otolith interactions, would be affected by exposure to space. Diminished accuracy of eye movement control during head movement may result. Thus, in space, adaptive vestibular changes can lead to alterations in behavior and performance, as well as to changes in perception of spatial orientation. Such adaptive alterations can in turn produce difficulties when the individual returns to an Earth gravity environment.

Related Topics

The topics of development and aging, neural modeling and neurotransmitters and molecular biology relate to the four areas discussed in each section of this report, e.g., signal transduction by vestibular end-organs; reflex control of posture and gaze; sensory integration in spatial orientation, perception and motion sickness; and adaptive changes in vestibular function.

Development and Aging

The major goal of developmental studies of the vestibular system is to enhance the understanding of the cellular and molecular events leading to neuron proliferation, migration, differentiation and synapse formation. These activities are essential for neuron precursors to become vestibular neurons. In contrast, aging studies focus on postmaturational changes that may result in diminished function and/or cell death. Both types of studies are needed to gain a better understanding of how the brain processes vestibular signals and adapts to change.

One of the major challenges confronting developmental neurobiologists is to understand how connectivity and synaptic specificity are achieved. These issues are confounded in the vestibular system by the highly complex central vestibular network that relies on multisensory inputs for its normal activity and is composed of a highly interconnected network of neurons, with less topologic organization than in other sensory systems. However, there are advantages to the developmental approach which begins by looking at neurons and their connections when the basic components of their organization and function are simpler and more readily apparent. Examining progressively older neurons and their more complex assemblies should result in further insights into how the system works. Studies of aging vestibular systems should enable us to determine whether the decline in vestibular function is a result of preprogramming (i.e., genetic influences) or the inability of the cells to sustain normal functional demands.

Following injury, the response of the adult vestibular system is characterized by a variety of responses which are species- and age-dependent. In lower vertebrates, hair cells in the inner ear and the vestibular nerve neurons have the capacity to regenerate. This capacity has not yet been demonstrated in mammals. Following the sectioning of amphibian axons, vestibular ganglion cells innervating individual receptor organs find their synaptic locus in the vestibular nuclei. The new connections are functionally operative suggesting that their reestablishment and neuromodulatory function must be genetically imprinted. The central nervous system can compensate for deficits in vestibular function, and this capacity is greatest in primates, including man. Vision has been recognized as an important component in the compensation of VORs of primates and other mammals. There is a paucity of information, however, about the cellular and molecular mechanisms of the repair process. Such mechanisms are being recognized in new experimental work.

Neural Modeling

Because of the ability to measure precisely ocular motor and, to some extent, postural compensation in response to vestibular stimulation, mathematical modeling of these systems is an important method for relating their reflex behavior to the neural components that determine that behavior. Dynamic system models have contributed to defining the parameters that characterize the vestibular system. For example, the characterization of the dominant behavior of the VOR and certain postural responses in terms of time constants is a direct consequence of approximating the systems as first-order linear systems. Extensions of these concepts have led to defining parameters of VOR behavior in three dimensions and have given rise to model-based studies that relate these parameters to fundamental organizational principles that determine the behavior of the VOR. Computational models and techniques that predict experimentally obtained, behavioral results and uncover organizational principles that govern vestibular-induced behavior are needed.

Problems concerning integration of information from the vestibular end-organs and reflex pathways, as well as from other sensory systems, are important to study as a component of vestibular research of balance and posture, both in the civilian sector and in aerospace biomedical research. Computer modeling of neural network function is an important and indispensable tool for understanding how ensembles of neurons produce the required integration of information and generation of motor responses.

Theoretical neurocomputing studies also confront this key problem of information processing (sensory fusion) that has been solved by the brain in the vestibular system. The issue of information integration from different sensors is common to biomedical research, aerospace biology and neurocomputing research. Cooperation among fields will optimize success in each. This success can be achieved by identifying or creating research facilities that can integrate such multidisciplinary efforts.

Neurotransmitters and Molecular Biology

Transmission of vestibular signals from the ear to the brain is initiated when hair cells release molecules of neurotransmitters which react with receptors on the membrane of afferent nerve fibers. Several animal models have demonstrated central nervous system control of labyrinthine receptors by efferent fibers transmitting via acetylcholine. However, despite the identification of glutamate, histamine and other agents as potential afferent transmitters, conclusive evidence that any of these compounds serves as a primary neurotransmitter is still lacking.

It is important to characterize the nature of vestibular neurotransmitters and modulators and their interactions. Motor learning and motor control require continuous remodeling (adaptive plasticity) of neuronal connections and neurotransmission in central vestibular pathways. Understanding the molecular biology and pharmacology of those processes is an important future goal.

Understanding Pathophysiology

Our knowledge of the pathophysiology of many human vestibular disorders comes from experimental observations of the anatomy and physiology of the system together with careful clinical observations and pathologic examination of human temporal bones and the central nervous system. The various mechanisms by which abnormal conditions may disturb the normal structure and function of the vestibular system can be categorized as: traumatic, inflammatory, degenerative, metabolic or neoplastic. These mechanisms may affect the end-organ and/or the vestibular nerve and brain as indicated below:

Trauma to the head may produce fractures or concussions which affect the inner ear or brain. Abnormal stimulation of the end-organ may be associated with otic capsule fistulization from bone resorption, change in the density of a cupula (cupulolithiasis) or an excessively long stapedectomy prosthesis.

Inflammatory destruction (labyrinthitis) is caused by bacterial or viral agents and immune disorders.

Degeneration of the end-organ may be produced by trauma, ototoxic antibiotics (aminoglycosides) and other drugs (loop diuretics, cis-platinum), vascular insufficiency (hemorrhages, infarction), hereditary disorders (Alport's syndrome, Waardenburg's syndrome) or surgical destruction (labyrinthectomy).

Metabolic disorders like diabetes mellitus, hypothyroidism, alcoholism or Paget's disease affect the vestibular system. Metabolic alteration (disturbed labyrinthine fluid composition or function) is commonly considered to be the mechanism by which Meniere's disease and serous labyrinthitis affect the vestibular system.

Neoplastic alteration of the nerve fibers near the end-organ may be caused by an intra-labyrinthine schwannoma.

At the vestibular nerve level, trauma may be caused by mechanical compression resulting from arachnoid cysts, arterial loops and bone tumors. Inflammatory change is recognized as the pathologic alteration produced by viral and bacterial agents (vestibular neuronitis). Degenerative changes are associated with demyelinating disorders, such as multiple sclerosis and surgical transection. Neoplastic alteration is most commonly produced by benign tumors (vestibular schwannoma) but may also be associated with metastatic malignancies from other organs.

A variety of neurogenic disorders affect balance and different aspects of brain functions related to vestibular function, such as the control of gaze and posture. These include: hereditary and developmental disorders (congenital nystagmus, migraine, Chiari malformation); several familial ataxia syndromes involving different parts of the cerebellum; degenerative disorders (multiple sclerosis, progressive supranuclear palsies); various neoplastic lesions; vascular disorders, particularly of the brain stem and cerebellum (vascular malformation, infarctions and hemorrhages); and autoimmune disorders, including paraneoplastic syndromes.

Recent Accomplishments

Understanding the Molecular, Cellular and Neural Basis of Peripheral and Central Vestibular Function

Signal Transduction by Vestibular End-Organs

Recent technical advances in membrane biophysics have been applied to hair cells with the result that we now have a qualitative understanding of the events that link the bending of sensory hair bundles with the modulation of afferent impulse activity. Detailed studies in a few end-organs have shown how the various steps in the transduction process can be modified so that different hair cells and afferents become selectively tuned to certain aspects of the mechanical stimulus.

Afferent nerve fibers innervating a particular end-organ differ in their response properties. By the anatomic labeling of individual, physiologically characterized fibers, it has been possible to relate this response diversity to the innervation patterns of the afferents, including their location in the sensory epithelium and the types and number of hair cells that they contact.

Information has been obtained about the response of single vestibular afferent fibers to electrical activation of the efferent axons originating in the brain stem. Studies in alert animals have begun to suggest how efferent activity can modulate afferent discharge under physiological conditions. In addition to classical neurotransmitters such as acetylcholine, efferent neurons contain a variety of neuropeptides and transmitters (metenkephalin and calcitonin gene-related peptide) that may influence receptor cells and afferent fibers in the end-organs.

Reflex Control of Posture and Gaze

Over the past five years considerable progress has been made in characterizing the sensory-to-motor transformations that occur in postural and gaze stabilizing reflexes:

- The patterns of limb, trunk and neck muscle activation by postural reflexes have been described and the ways in which they vary with context are being explored.
- Descriptions of the dynamic and three-dimensional spatial transformations that occur in vestibulo-ocular and vestibulo-collic reflexes have been obtained. The patterns of muscle activation that result have been described and models have been advanced that successfully predict the muscle patterns that are used during the VOR and vestibulo-collic reflex.
- Information has been obtained in humans and non-human primates on VORs and their interactions with vision in response to linear acceleration. Eye movement control has been shown to involve interactions among otolith, visual and vergence mechanisms, and further understanding of such control mechanisms should lead to the rationale for quantitative tools for clinical assessment of otolith function.
- While understanding of the neuronal substrates of postural reflexes is at a rudimentary stage, great progress has been made in discovering the neural connections that mediate the transformations that occur in gaze-stabilizing reflexes.
- The structure and function of vestibulo-ocular relay neurons that form the middle portion of three-neuron VOR arcs have been described in sufficient detail to reveal how convergent labyrinthine inputs to these neurons and their divergent projections to multiple motor pools could contribute to reflex transformations. Neural network models that explore these possibilities in a formal way are beginning to appear.

- Beginnings have also been made in describing the more complex indirect pathways that contribute to the VOR and in determining how both direct and indirect pathways may be regulated by the cerebellum.
- Research has begun to define the biophysics and pharmacology of neurons in vestibular reflex pathways.

Sensory Integration in Spatial Orientation, Perception and Motion Sickness

Originally, vestibular reflexes were conceived as being automatic and not subject to cognitive control. However, recent research has shown that we can use information from vestibular receptors during movement to determine where we started from and how far we have moved. We can also use the imagined location of near and far targets to adjust the magnitude of eye movements that compensate for linear or angular head movements. Thus, cognitive processing of vestibular information is not only important for determining spatial orientation but also for establishing proper control of VORs.

Great strides have been made in understanding the compensatory responses produced by the otolith organs during linear head movements by considering the eye movements that would be necessary to view real or imagined visual targets. Slower or faster eye movements are required depending on whether targets are far or near. These compensatory eye movements even occur when targets are imagined in darkness.

Studies of this nature have revealed that the VOR is not a simple semicircular canal-mediated response. Instead it encompasses a broad range of reflex responses originating from each of the motion sensors in the labyrinth. Inputs from these sensors are directed toward the vestibular nuclei, where they are integrated with information from the visual and somatosensory systems and from proprioceptors to form signals that direct gaze movements and stabilize posture and equilibrium. Cerebellar participation is essential for proper operation of these vestibular reflexes.

Models of the VOR and of vestibular compensatory eye movements have shown that there are at least two components to the reflex. One operates rapidly to produce quick changes in eye position and eye movement in response to head movement. The other has more sluggish characteristics but outlasts impulses of acceleration and is largely responsible for the characteristics of eye movements induced by rotation. This component has recently been shown to be oriented around gravity. Both components are subject to adaptation, and these types of motor learning are controlled by various portions of the vestibulo-cerebellum. Lesions of the cerebellum cause deficits in compensatory movements, as well as disorientation and dysequilibrium.

The current theory of motion sickness holds that it is a by-product of the process of adaptation to unusual sensory inputs or motion conditions. It has been demonstrated that subjects have a remarkable ability to adapt to unusual motion conditions, although the process of adaptation is often associated with motion sickness. When adaptation is finally achieved, the vertigo and/or motion sickness disappears.

Adaptive Changes in Vestibular Function

As described above, the vestibular and balance control systems have the remarkable ability to maintain useful function in many novel motion environments and to adapt to abnormal function of one or more of their components. The ability of these systems to adapt systematically sensory, neural and motor components in order to achieve useful compensation must be more thoroughly understood. Advances in vestibular health care, particularly rehabilitation, should be developed from sound scientific concepts. Therefore, the significance of central nervous system phenomena associated with the adaptive process (such as neural sprouting, reactive synaptogenesis and long-term potentiation or depression of synaptic transmission), which are thought to play important roles in adaptive control, must be measured and correlated systematically with behavior. Some accomplishments that have opened exciting new areas of investigation include:

- The essential role of adaptive plasticity in normal function of the vestibular system has been recognized. This system is unusual in that it is not static. It is constantly changing in response to changes in the environment or internal elements (for example, inner-ear or central nervous system diseases).
- Neural pathways that may play a role in adaptive changes have been identified. As indicated above, there are several possible models of the neural basis of VOR plasticity. Information is also beginning to emerge about the neural changes that accompany recovery from unilateral labyrinthectomy.
- The pharmacologic aspects of adaptive changes and their roles in transmitter synthesis as well as the release, number and sensitivity of receptors have been described.

Research from both U.S. and Soviet space flights has shown alterations in eye movement and postural control, as well as in perception of spatial orientation, both during flight and after return to Earth. It appears that the plasticity of vestibular reflexes, for the most part, allows adaptation during short duration missions, but the effects of vestibular system performance after long exposures is unknown. The precise characteristics of adaptive plasticity in this unique environment and the vestibular function involved in readaptation to Earth's gravity after long-duration exposure to space remain unknown. Vestibular and balance system adaptation to altered gravito-inertial environments has not been measured systematically.

Related Topics

Development and Aging

Recent work suggests that a synchrony may exist between structural maturation of the vestibular end-organs and central vestibular nuclei. In recent developmental studies of the vestibular system, classical approaches have been supplemented with molecular biological probes and innovative techniques. For example, connectivity of the vestibulo-ocular and vestibulo-spinal pathways has been studied by the application of fluorescent dyes (e.g., Lucifer yellow, carbocyanine) in brain slices and on cultured brain stem and spinal cord preparations; immunocytochemical probes are used to examine the vestibular pathways and the maturation of otolith organs; and brain slice preparations are employed to obtain membrane and synaptic properties of developing vestibular sensory neurons.

From the combination of electron microscopic methods and tract tracing techniques, we are beginning to determine the steps in the assembly of synaptic inputs to the vestibular brain stem nuclei. Specifically, the first synapses formed in the chick's lateral vestibular nucleus are not formed by primary vestibular fibers but appear to be derived from fibers of central origins. It is important to determine the steps in the assembly of various synaptic inputs to vestibular neurons in order to test what role synaptic formation may play in orchestrating developmental events.

The aging vestibular system also shows interesting changes in the structure of sensory and non-sensory components. Senescence has long been associated with increased vestibular dysfunction in older subjects who have more difficulty with vestibular test performance than younger subjects. Animal studies indicate that neural vestibular components in the ear and brain tend to accumulate a so-called aging pigment or lipofuscin. This and related substances, accumulated during the process of aging, may place a burden on the normal functioning of neurons and may diminish their response to functional demands. The characteristics of structural, functional and behavioral modifications of the aging vestibular system need to be studied. We need to determine if diminished efficiency with age is due to irreversible preprogrammed cessation of function or to reversible cellular modifications.

Neural Modeling

In the past decade, there has been increasing interest in mathematical modeling of vestibular systems at the level of the end-organ, neural pathways and reflex behavior. Models are important because they formalize concepts, organize data and predict responses. Modeling reflex behavior by applying control system analysis, as developed and used in electrical engineering, has been augmented by developing mathematical descriptions of the functioning of parallel neural networks. This conceptual advance is important because it shows that it is possible to reproduce neural behavior by layers of interactive adapting elements. The vestibular system is a natural entry point for the use of such models linking biological and theoretical neural network approaches.

It is not sufficient merely to set up neural networks with a multitude of parameters and adapt them to fit arbitrary data. Studies need to be conducted to derive learning algorithms from fundamental principles that are consistent with mathematically formalized, behavioral constraints. Using realistic models of cellular dynamics as derived from pharmacodynamics could also be helpful in uncovering the principles that govern behavioral learning in the vestibular system such as adaptation and habituation.

Neurotransmitters and Molecular Biology

Considerable progress has been made in identifying the neurotransmitters involved in the vestibular system. The field of potential primary hair cell neurotransmitters has been narrowed to glutamate-related excitatory amino acids. The transmitters liberated from the eighth nerve fibers onto brain stem neurons have not yet been specified, but the inhibitory transmitters of the vestibular commissural systems include gamma-amino-butyric acid and glycine. Since data from recent studies on other systems indicate that several neurotransmitters may coexist in the same synapse, this possibility should be investigated in the vestibular system.

Advances in Diagnosis

Thoughtful history taking based on a knowledge of the anatomy, physiology and pathology of the vestibular system provides the core of diagnostic information necessary for clinical practice. This information is enhanced by tests which describe the integrity of vestibular reflexes.

Testing - Physical

Advances in modern technology have made the evaluation of vestibular patients a quantitative science. Because the VOR is the best understood vestibular reflex, scientists have taken advantage of the reliability of eye movement measurement to develop a battery of vestibular function tests to study the integrity of the various VORs.

The function of the cristae of the horizontal semicircular canals, sensors for angular acceleration, can be measured with the caloric test by irrigating, under precisely controlled conditions, the external ear canal with water at different temperatures. The resulting eye movements can be accurately and efficiently measured with the aid of small laboratory computers.

Other methods of evaluating semicircular canal function include the use of rotary platforms and measurements of VOR responses to obtain precise information about the relationship between stimuli and reflex eye movements.

The function of the linear acceleration sensors of the ear (the otolithic organs) has been measured by observing ocular reflex responses to stimulation with various devices including the parallel swing. Also, the evaluation of balance has improved greatly with the use of platforms which measure movement of the patient's center of mass with sensitive force transducers whose signals are analyzed by computer.

The contribution of the visual system to orientation is evaluated by measurement of visual oculomotor reflexes, including the use of tests for smooth pursuit function and optokinetic nystagmus. These tests evaluate the ability of patients to follow small visual images (the smooth pursuit system) or the movement of large visual scenery (optokinetic function). The most revealing information is obtained by combining visual with vestibular stimulation as described above. Given the extent of neural pathways subserving vestibulo-ocular and visuo-oculomotor reflexes, information from these tests provide methods to evaluate large areas of the brain. The combination of such tests in the modern vestibular test battery has allowed the identification of the location within inner ear or specific brain regions of vestibular lesions, a quantitative estimate of the magnitude of the deficit and the ability to follow the course of the disease. Useful features of these tests are their non-invasive nature, their ease of administration and minimal discomfort for the patient.

In addition to these standard tests, new tests are being developed in animal studies and being investigated in humans. Several of the new human vestibular tests are designed to evaluate anterior and posterior semicircular canal function (in addition to horizontal canal function) by rotating subjects about different axes to optimize stimulation of the specific canals. A problem associated with attempts to activate vertical canals is the simultaneous stimulation of the otolithic organs and the complexity of measuring the resulting eye movement. New methods, such as video-based monitors, are being developed to deal with the latter problem.

Of all the available vestibular tests, only the caloric test allows specific location of a lesion in one of the ears. All other tests using physiologic stimuli represent the response of a multiplicity of nerve centers. In recent years, however, animal experiments have provided information that suggests the possibility of evaluating lesions specifically located in the vestibular nerve. Vestibular-evoked potentials have been obtained from the nerves of the semicircular and otolith organs in several animal species. Responses from direct electrical stimulation of the vestibular nerve also have been obtained in animal and human experiments.

A major deficiency is the lack of tests for otolithic and proprioceptive reflexes. Tests are being developed to evaluate these systems under operational conditions in freely moving animals and human subjects. There is interest in the evaluation of head and eye interactions in humans with normal and abnormal vestibular function. Also lacking are tests for the quantitative evaluation of the subjective sensation of motion and of dizziness in patients.

Also, there are no tests that allow the physician to assess the possible role of neck muscle or bone lesions in the production of dizziness, vertigo or postural imbalance.

Testing - Laboratory/Radiology

Tests for antibodies to inner-ear antigens have recently been developed and appear to help in the diagnosis of inner ear autoimmune disease.

Fine resolution imaging has improved with the development of better software and technology for both computed tomography (CT) and magnetic resonance (MR) scanning. Improved use of contrast and speed of image acquisition have made it possible to detect smaller lesions and permit dynamic CT/MR scanning to evaluate blood flow in small regions of the central nervous system. The development of techniques for imaging the individual receptors in the labyrinth would improve diagnosis and understanding of the disease process.

Advances in Treatment

Medical Therapy

Advances in basic research have identified probable transmitters and receptor sites in the vestibular periphery and central connections. These findings have not only led to clinical trials of transmitter agonists and antagonists but have also resulted in the realization that most pharmacologic agents with potential central nervous system activity may interfere with normal vestibular function. For example, long-acting sleeping pills and tranquilizers are now recognized as a major cause of injuries from falling in nursing home patients.

Clinical trials of antihistamines, anticholinergics and phenothiazines with improved experimental design have been conducted, and these agents appear to be helpful in relieving the symptoms of vertigo. Unfortunately, these agents have side effects such as drowsiness and dry mouth and eyes.

The reduction of symptoms, presumably related to increased endolymph fluid, with systemic diuretics appears to be helpful, at least in the early stages of Meniere's disease.

Further studies using systemic, transtympanic or intralabyrinthine aminoglycosides show good results in reducing vertiginous attacks in patients with Meniere's disease but have the potential side effects of loss of hearing or severe loss of vestibular function and oscillopsia (a condition in which objects appear to move up and down or from side to side).

The recognition of the relationship between associated disorders such as depression, anxiety attacks and panic attacks and vestibular disorders suggests the need to investigate these disorders as well. Recent advances in the pharmacologic control of these disorders is encouraging.

Surgical Therapy

Surgical treatment strategies in peripheral vestibular disorders may be grouped into ablative and non-ablative protocols. Ablation procedures relieve the balance symptoms by denervating the altered labyrinth without correcting the lesion. These procedures are 90 to 99 percent effective in relieving episodic dizziness provided that the ablation is complete. If hearing is not useful in the unilaterally diseased ear, labyrinthectomy (transcanal or transmastoid approach), is a short, relatively safe technique. If there is useful hearing in an unilaterally affected ear, selective vestibular neurectomy, via a middle cranial fossa (MF) or posterior cranial fossa (PF) approach, is now the accepted procedure. The MF approach is technically more difficult and is associated with a higher incidence (25 percent) of temporary facial nerve weakness than the PF approach. However, it has a higher success rate (95 to 98 percent) for vertigo control than the PF method (80 to 90 percent) because of the natural separation of the vestibular and auditory nerves in the internal auditory canal. The separation of these two groups of fibers in the posterior fossa section of the eighth nerve is arbitrarily created by the surgeon.

Selective transection of the posterior ampullary (singular) nerve has been successful in more than 90 percent of patients with chronic disabling positional vertigo (cupulolithiasis). Associated sensorineural hearing loss has occurred in fewer than five percent of the cases.

Non-ablative procedures correct the pathologic derangement responsible for altered vestibular function. Several examples of these are: removal of chronic inflammatory tissue (cholesteatoma) from a bony semicircular canal fistula, removal of an excessively long stapedectomy prosthesis, removal of chronic inflammatory tissue from the oval and round windows and repair of a perilymphatic fistula in the oval or round windows caused by direct or indirect trauma.

The efficacy of vessel loop relocation from the intracranial portion of the eighth nerve has been variable and remains undetermined at this time.

Rehabilitation

The use of exercises to improve gaze and postural stability in patients with vestibular disorders has become increasingly popular in the past five years. The exercises are based in part on anecdotal evidence of improved function in patients following exercise intervention. The exercises are also based on the results of animal research demonstrating that visuo-motor experience can increase the rate of recovery following unilateral vestibular loss and that preventing visual inputs or movement can delay the onset of recovery. Research on human subjects is in progress, but the results are not yet known.

Outcome measures of treatment efficacy include many of the standard methods for quantifying balance but are often dependent on subjective reports. A questionnaire that measures the patient's perception of the extent to which the vestibular or balance disorder is handicapping has been developed and validated.

Program Goals

There is a need to expand the knowledge of normal and abnormal structure and function of the vestibular system using recently developed techniques in a broad spectrum of scientific disciplines. Scientists must be trained and research support provided to establish a knowledge base commensurate with other fields of medicine. In order to achieve this goal there must be increased study of both human pathologic material and animal studies.

Understanding the Molecular, Cellular and Neural Basis of Pheripheral and Central Vestibular Function

Sensorimotor systems such as the vestibular system depend upon the integration of information from many sensory sources which must be transformed to control many different muscle groups, thus posing a unique experimental challenge. Vestibular functions, especially those involved in stabilizing gaze, are sufficiently simple and stereotyped in their action to raise the hope that vestibular research will yield the first breakthrough in understanding a complete sensorimotor system and major advances in understanding clinical problems. To achieve this goal a broad array of modern molecular, pharmacological, biophysical, anatomical, physiological, psychophysical and kinesiological techniques need to be mobilized to study the system at the subcellular, biophysical, neural circuit, perceptual and behavioral levels. Data obtained from these studies must be integrated into detailed computational models that will permit the knowledge of the system to be tested and used to predict outcomes of new basic and clinical experiments.

Signal Transduction by Vestibular End-Organs

At the level of the vestibular end-organs, the overall goal is to understand the response of vestibular nerve fibers in terms of cellular mechanisms, which in turn must be related to cupular and otolithic membrane dynamics. This understanding will require detailed studies of the sensory epithelium, including hair cells and their afferent and efferent innervation. Since afferent nerve fibers which innervate different parts of an end-organ vary in their properties, it will be important to study mechanisms on a regional basis. The following goals have been identified:

- Use advanced imaging techniques to study the mechanics of the cupulae and otolithic membranes and the hair bundle attachments to them. Relate the mechanical properties to the physical and molecular properties of these structures.
- Relate the biophysical properties of the transduction channel to the ultrastructure of the hair bundle and to biochemical events taking place in the cilia. Develop the biochemical techniques needed to isolate and characterize the molecular components of the transduction channel and the associated regulatory proteins.
- Characterize the biophysics and cellular biology of hair cells and afferent terminals, relating them to their location in the sensory epithelium and to the structure of the hair cells (Type I or Type II).
- Study the pharmacology and biochemistry of afferent and efferent neurotransmitters. Use recently developed techniques of chemical neuroanatomy to determine if there are several populations of afferent or efferent neurons which are distinguishable on the basis of their transmitter biochemistry.
- Define the role of efferent neurons, including an analysis of the effects of efferent activation on receptors and afferent synapses. Afferent-efferent interactions need to be understood in terms of electrical,

chemical, metabolic and neuromodulatory mechanisms. Use alert animals to determine the behavioral conditions that lead to changes in efferent activity, to characterize the profile of the resulting changes and to investigate their influence on the end-organ.

- Develop experimental models for peripheral vestibular dysfunction, taking advantage of species differences and genetic variations.

- Characterize the mechanisms regulating fluid, electrolytes and metabolites of the inner ear.

Reflex Control of Posture and Gaze

There is a need for further understanding of the reflexes associated with posture and gaze at the neural circuit level, including the basic reflex connections and the more complex pathways that supplement and modulate their actions. The overall goal is to mount a comprehensive, interdisciplinary initiative to understand the function of these critical reflexes. Some specific goals are:

- Undertake a comprehensive analysis of the neuron populations that participate in gaze-stabilizing reflexes in order to correlate their biophysical and pharmacological properties with their structure and function.

- Identify with anatomic and physiologic techniques the neural substrates of vestibular reflexes acting on neck, axial and limb musculature.

- Develop computational models that will foster understanding of how populations of neurons can implement postural and gaze reflexes.

- Determine at the behavioral level, which strategies the central nervous system uses to control movement and posture. Define the relative roles played by sensory inputs from semicircular canals, otolithic organs, neck muscle proprioceptors and the eyes in determining the dynamic and spatial characteristics of movement.

- Determine the discrete or continuous nature of sensory-to-motor transformations in postural reflexes of animal and human subjects. Undertake experiments to record neural activity related to these reflexes in animals.

- Define the mechanisms underlying otolithic organ control of eye movements and how they are integrated with visual mechanisms, particularly during linear accelerations that occur during normal behaviors, such as locomotion and postural sway. Determine how otolithic organ and semicircular canal control of eye movements interact during the complex motions that include components of linear and angular motion.

- Develop tools for the quantitative assessment of otolithic organs' function in normal persons and in those with clinical indications of vestibular malfunction.

Sensory Integration in Spatial Orientation, Perception and Motion Sickness

Natural Motion Versus Passive Motion

The role of the VOR is to stabilize gaze so that images can be held on the retina and seen. To date, most studies of the VOR have been performed by rotating subjects with their heads and bodies fixed. However, the vestibular system works in freely moving individuals who are changing both head and eye positions. Although it is technically difficult, it is essential that we address the problem of gaze stabilization in freely-moving subjects to gain a full appreciation of the range and capability of the vestibular system. Only when we study the vestibular system in its natural state will we begin to understand the nature of the deficits that occur after unilateral and bilateral peripheral vestibular disease and central vestibular or cerebellar disease or in aging. These studies should be conducted in animal and human subjects who are engaged in full-body movement while their eyeand head movements and single-unit activity from the brain stem are monitored. Reactions produced by controlled-passive head and body movement should be compared with reactions in freey moving subjects.

Processing and Modeling of the Vestibulo-Spinal System

A particularly important aspect of otolithic-vestibular, nuclear and vestibulo-cerebellar processing is that information about upright stance and balance is created from otolithic organs and other signals that provide a sense of the upright and from the feedback information from joint and muscle proprioceptors. It is critical to have a better understanding of the various parts of the vestibulo-spinal system. At least part of the problem is that there has been little attempt to model the vestibulo-spinal system other than to predict muscles that would be activated by individual semicircular canals during natural head movements. We need dynamic models that match the characteristics of the output signals to the characteristics of the body part upon which the vestibular signals operate.

Neural Basis for Spatial Orientation

Orientation in space is a complex function that involves the vestibular system as well as cerebral structures and cognition. The neural basis for spatial orientation is poorly understood, and promising leads obtained from blood flow studies, single-unit studies and the results of specific lesions should be pursued to enlarge our conceptual models of this important area.

Motion Sickness

Central nervous system changes in cellular and hormonal activity associated with motion sickness must be characterized in appropriate animal models and humans.

Adaptive Changes in Vestibular Function

If we are to harness the capabilities of the adaptive system to optimize vestibular function at all ages and to restore function after peripheral or central lesions, we must more fully understand its operation at the behavioral and neural levels.

At the behavioral level we need to:

- o Develop an understanding of the physical stimuli that govern adaptive behavior. For instance, evaluate the relative roles of inputs from central versus peripheral retinal receptors, inputs from various vestibular end-organs and inputs created by active versus passive motion.
- o Understand what aspects of such vestibular performances as reflex size or timing, perception of space or motion and regulation of static and dynamic posture can be altered by the adaptive system.
- o Investigate the ability of the vestibular system to adapt to special environments, such as under water, high performance aircraft and the various conditions of space flight.

At the neural level, we must define the anatomical, physiological and biochemical changes in specific neural circuits that underlie adaptive behavior and develop models for systematic investigation of how such neural changes can contribute to compensation for functional deficits in the vestibular system. Three sequential goals for achieving this are:

- o Determine at which site(s) the neural changes responsible for adaptation occur using anatomic, histologic and physiologic techniques.
- o Analyze the biophysical, pharmacological and molecular bases of these changes and evaluate the possibility of manipulating them therapeutically.
- o Develop neural network models which determine whether the observed neural changes are sufficient to explain adaptive vestibular performance and to predict the effects of various therapeutic interventions on adaptive performance.

In addition, further research is necessary to understand the cellular source of the slow and rapid components of the VOR, how the different areas of the vestibulo-cerebellum are interrelated and the cellular mechanisms of their action. An understanding of the motor learning that is involved in control of both the rapid and slow components of the VOR is likely to involve an understanding of how the mossy fiber input and climbing fiber systems originating in the inferior olive interact with Purkinje cells. Only when these interactive loops are understood will we be able to model and predict the adaptive capability of individuals to alter their responses to changing visual and vestibular inputs, including altered gravitational environments and after unilateral and bilateral disease of the labyrinth.

Model validation must proceed at all levels (neural, sensory, motor, perceptual and behavioral). Modeling is an excellent way to organize our thinking about the dynamics of the interactions we seek to understand. New and potentially more powerful approaches to mathematical modeling are to be encouraged along with continued reexamination of existing models in the light of new experimental data.

Related Topics

Development and Aging

A central issue in developmental neurobiology is the interdependence of axons and the neurons they innervate and how this relationship is influenced by growth, experience, injury and aging. To understand assembly of the vestibular system, systematic studies are required to define the sequence of innervation and synapse formation on central vestibular neurons. Specific issues are:

- Study the onset of signal processing in the vestibular system during development and the correspondence between peripheral and central structural changes leading to the onset of vestibular function.
- Determine the role of neurotransmitters and neural activity in vestibular neuron development (at the level of identified cells).
- Study the emerging membrane properties of identified vestibular neurons.
- Study the responses of developing vestibular neurons to vestibular and non-vestibular stimulations. Studies should be performed on both normal developing neurons and those in partially deafferented brains.
- Compare the morphogenetic and electrophysical relations between vestibular axons and Type I and Type II hair cells in the end-organ and examine how peripheral structure changes during

synaptogenesis in the developing labyrinth.

- Compare central nervous system and peripheral nervous system synaptic interactions to determine what factors influence development at different ages, focusing on critical periods of development.

- Determine the onset and progression of sensory integration of inputs from specific vestibular end-organs to vestibular neurons in the brain stem. This time course should be related to the functional changes in vestibulo-ocular and vestibulo-spinal reflexes as a function of age.

- Determine the behavioral changes associated with the aging process and design strategies for preventive and rehabilitative intervention.

- Determine the anatomical and biochemical changes associated with aging at various parts of the reflex. This study should include the quantification of cellular changes in the receptor organs (sensory and supporting structures), primary afferents, vestibular nucleus neurons and motor efferent elements.

- Study the differential role of aging in the various cellular elements of the vestibular reflex to find familial and idiopathic causes of premature aging in the inner ears and central vestibular centers.

- Use animal models, including mutational variations, to elucidate the causes and course of the aging process.

Neural Modeling

Impressive strides have been made in understanding areas of the vestibular system where it has been possible to model the neural input and output, thereby formalizing the transfer functions that are performed by the central nervous system. There is a continuing need to model the VOR and perceptual-motor responses to various combinations of semicircular canal and otolithic organ stimulation. In addition to animal models and human pathologic material, concentrated efforts must be made to develop mathematical and computer models to complement and supplement ongoing experiments.

Wherever possible, strategies that the central nervous system uses to control movement and posture should be defined using mathematical and computational paradigms and models at the behavioral level, as well as at the level of neuronal networks and single neurons. Specific goals are to:

- Develop mathematical and computer models for systematic integration of the knowledge base on vestibular function and adaptation into a formal understanding of the function of vestibular neural networks.

- Develop cooperative studies to investigate vestibular and balance problems in special environments, such as underwater, aviation and aerospace. Incorporate mathematical-computer modeling of vestibular systems with the goal of integrating experimental knowledge into a theoretical understanding of the brain as a neurocomputer.

- Seek experimental verification of models under simple as well as complex conditions of motion.

Neurotransmitters and Molecular Biology

The molecular properties of neurotransmitters of the vestibular system should be investigated. Multidisciplinary approaches should be combined in the same animals, whenever possible, in order to delineate cause and effect relationships. Use should be made of animal and human material to study the presence of neurotransmitters in adult subjects as well as during development. Modern techniques for neurotransmitter identification (e.g., in situ hybridization) and immunochemistry should be combined to elucidate the synaptic processes and their development. Specific questions requiring investigation are:

- Characterize molecules released in response to electrical and chemical stimulation with pharmacologic and molecular techniques.

- Examine molecular changes that accompany documented and measurable deficits in vitro and in animal models to determine their relationship to the deficits, causal or not, and their mechanism of action.

- Document coexistence of multiple molecules with neurotransmitter and neuromodulator properties in individual neurons. Their interactions should be investigated.

- Perform experiments using agonist and antagonist substances to presumptive neurotransmitters using in vitro and in vivo preparations.

- Develop monoclonal and polyclonal antibodies to newly identified neurotransmitters to determine their cellular localization by means of immunocytochemistry.

- Study changes in gene expression in vestibular neurons during development, aging and plastic, adaptive alteration of vestibular function.

Understanding Pathophysiology

- Acquire human tissues such as temporal bone and central nervous system structures from normal subjects and patients with documented vestibular symptoms and study the tissues by means of light microscopy, transmission electron microscopy, scanning electron microscopy and cytochemical methods.
- Develop and study animal models to provide insight into diseases that currently are incompletely explained, such as vessel loop compression of the vestibular nerve and metabolic effects of endocrine disorders.
- Study the effects of compromising the blood supply to vestibular sense organs. This study should be preceded by a description of the vascular supply and flow to the vestibular labyrinth.
- Study the effects of specific vestibular lesions in animal models.
- Encourage young histopathologists and provide training in peripheral and central vestibular system pathology.

Needs in Diagnosis

The overall objective of vestibular testing is to utilize an efficient battery of tests to determine the site and severity of a lesion. This battery should be a quick, efficient set of tests that minimize the time and cost to the patient and optimize the diagnostic value to the physician. Research goals in this area include the need to:

- Develop standards, by age group, for the more commonly used diagnostic techniques including caloric, rotational and posturographic tests. No acceptable or standardized methods have been established for these tests and variations in the methods used in different centers make it difficult to compare results.
- Use animal models and human subjects to develop new tests to evaluate all the recognized receptor organs in the vestibular apparatus. In particular, there is a need for simple and reliable tests of otolithic organ functions. There is a similar need for tests of vertical semicircular canal function.
- Develop psychophysical methods for evaluation of vestibular function in health and disease.

- Develop tests for alteration in neck and vestibular function and neck and vestibular interactions.
- Use animal models to study the pathophysiology of disease processes, such as Meniere's disease, vestibular neuronitis, positional vertigo, benign paroxysmal positional vertigo, unilateral and bilateral hypofunction and ototoxicity.
- Conduct serial studies of changes in vestibular test results in patients with well-defined pathologic processes including evaluation of the process of compensation and resulting changes in reflexes.
- Investigate the effect of pharmacologic therapy on the rate of recovery produced by compensatory processes.
- Develop diagnostic procedures to evaluate vestibular developmental processes by the study of patients with developmental disorders and animal models of genetic disorders with abnormal receptor function, e.g., use of animal mutants without otoliths.
- Investigate the pharmacologic, molecular and genetic basis of inner-ear disorders.
- Develop biochemical and histological methods to detect immunologic, autoimmune and neoplastic abnormalities in the inner ear and eighth nerve.
- Compare results of observations made in patients with central vestibular disorders to those made in patients with disorders of visual and motor function such as congenital nystagmus, other abnormalities of ocular stability and ataxic syndromes secondary to cerebellar degeneration using brain stem evoked response, visual evoked response and neural conduction velocity tests.
- Use postmortem material to confirm presumed diagnosis on longitudinally well-studied patients; evaluate test results for the identification of a known cause of disease; study patients with unknown causes; and investigate immunologic and molecular changes in the inner ear and central nervous system of patients with vestibular disorders.

Needs in Treatment

Medical Therapy

The goals of current medical therapy are to relieve symptoms and ameliorate aberant signals from an abnormal peripheral vestibular organ. Presently, all medicines which suppress vertigo and the associated autonomic symptoms have important side effects. They cause drowsiness, dry mouth and eyes and may interfere with normal central nervous system function. Therapeutic agents with greater specificity need to be developed. These developments should result from basic science experiments, for example employing monoclonal antibodies to locate specific receptor sites within vestibular pathways. Work should be continued on the following topics, and specific goals are to:

- Investigate neurotropic agents such as nerve growth factor and thyroid and adrenocortical stimulating hormones, showing some promise but not yet having been sufficiently evaluated to be recommended for clinical use.
- Determine the possible deleterious effect of vestibulo-suppressive medications on rehabilitation.
- Compare prospectively the effects of ablation with the effects of aminoglycosides.

Surgical Therapy

Work should be continued on the following topics, and specific goals are to:

- Evaluate, in carefully controlled, clinical studies, the effectiveness of controversial procedures, such as vessel loop relocation, perilymph fistula "repair" and canal "plugging" for benign paroxysmal positional vertigo. Animal models with documented histopathologic correlates of these lesions should be employed as well.
- Examine the anatomic and physiologic aspects of the central compensatory events that follow labyrinthectomy and vestibular neurectomy in animal models. Short- and long-term assessment of these changes may help to determine the optimal therapeutic procedure.

Rehabilitation

Work should be continued on the following topics, and specific goals are to:

- Determine whether exercise enhances vestibular rehabilitation and/or improves the level or rate of recovery in patients with vestibular disorders using prospectively controlled studies which quantify changes in vestibular function. The exercise approaches used should be founded on knowledge of the normal anatomy and physiology of the vestibular system and may be specific for different disorders.
- Develop outcome measures for assessing treatment efficacy, including postural responses.
- Investigate the effect of co-morbidity on recovery following vestibular lesions, especially the

effect of disorders that affect the visual and somatosensory systems.

- Determine the adaptive capability of the vestibular system in young and old subjects and patients with various vestibular disorders.

Research Opportunities

Major Basic Scientific Opportunities

There are five broad, high-priority areas for basic vestibular research: signal transduction by vestibular end-organs; reflex control of posture and gaze; sensory integration in spatial orientation, perception and motion sickness; adaptive changes in vestibular function; and development and aging of the vestibular system. Within each area opportunities exist for research at the levels of: behavior, kinesiology and biophysics; anatomy and physiology; cellular properties, biophysics and metabolism; pharmacology, molecular biology and genetics; and mathematical and computer modeling. These opportunities can be summarized as follows:

Signal Transduction by Vestibular End-Organs

Important goals are to understand how vestibular end-organs convert head movements into neural signals and to determine the way in which this conversion is modulated by efferent projections from the brain to the end-organs. Research is needed to:

- Describe the motions of the cupulae and otolithic membranes in response to head movements and examine the possible role of hair cell motility in modifying these motions.

- Determine the distribution and organization of otolithic organ and semicircular canal inputs to the vestibular nuclei and cerebellum and elucidate the function of the vestibular efferent system in behaving animals through anatomic and physiologic research.

- Characterize the biophysical properties of hair cells and afferent fiber terminals. This research should include studies of the hair cell transduction channel, the basolateral currents within hair cells and the efferent actions on both hair cells and afferent nerve terminals.

- Conduct molecular biological studies which isolate and characterize the molecular components of the transduction channel and associated regulatory proteins.
- Identify neurotransmitters which mediate peripheral vestibular function .
- Investigate metabolic requirements of the sensory organs and neurons in the inner ear and the mechanisms of production of inner-ear fluids and transduction elements (cristae and maculae).
- Develop dynamic models that predict and explain patterns of afferent fiber activation on the basis of anatomical and biophysical properties of end-organs.

Reflex Control of Posture and Gaze

The goal is to understand the structure and function of neural circuits that transform vestibular sensory input into the motor output required for control of posture, locomotion, fine motor activities and gaze. Research is needed to:

- Characterize the behavioral strategies and neural mechanisms used to determine posture and gaze during active and passive motion and during combinations of linear and angular acceleration in three dimensions. Studies are also needed to define the effect of exposure to altered gravito-inertial fields on vestibular reflexes and their potential clinical consequences.
- Characterize the anatomic and physiologic properties of neuronal pathways that constitute the vestibular system in animal models and normal humans. It is especially important to identify pathways involved in vestibular reflex control of neck, axial and limb muscles and to determine the signals they carry. Emphasis should also be given to understanding the neural substrates of otolithic organ reflexes and postural stabilization.
- Correlate structure and cytochemistry of neurons in different vestibular circuits with their response characteristics.
- Characterize the biophysical, molecular and pharmacological properties of specific groups of relay neurons in postural and gaze reflex pathways.
- Develop multidimensional models that explore the neural basis of dynamic and spatial transformations in vestibular reflexes.

Sensory Integration in Spatial Orientation, Perception and Motion Sickness

Understanding of the vestibular system requires knowledge of how vestibular signals interact with information from other senses to generate perceptions, movements and motion sickness. Research is needed to:

- Describe sensorimotor and perceptual reactions to complex combinations of linear and angular accelerations and determine how vestibular, visual and proprioceptive inputs interact to generate perceptions of space and body motion.
- Conduct anatomic and physiologic research to characterize the neural mechanisms that combine otolithic organ, semicircular canal, visual and somatosensory information to generate perceptual and postural responses and that generate motion sickness.
- Characterize the neural and humoral mechanisms associated with motion sickness and vertigo at the cellular and molecular levels.
- Develop models that incorporate and test the understanding of the neural basis of postural and gaze control during active and passive motion.

Adaptive Changes in Vestibular Function

Studies of vestibular adaptation can both reveal basic principles of motor learning and lead to strategies for enhancing recovery from vestibular lesions. Research is needed to:

- Determine at the behavioral level, both the extent to which the adaptive system can compensate for vestibular dysfunction and the sensory cues that are important in producing this compensation. Adaptive changes in both rapid and slow components of the VOR and in postural reflexes should be studied.
- Conduct anatomic and physiologic research to determine where in the brain stem and cerebellum the neural changes responsible for adaptive alteration of vestibular reflexes occur and how these changes lead to the observed alterations in behavior.
- Characterize the biophysical changes that occur at various neural sites during the adaptive process.
- Analyze the pharmacologic and molecular bases of adaptive changes and the way in which they depend on expression of molecular mechanisms such as proto-oncogenes, second messengers or humoral factors.

- Develop models that account for adaptive changes at both the biophysical and neural circuit levels.

Development and Aging of the Vestibular System

Knowledge in this area will both help us deal with developmental disorders and age-related declines in vestibular function and also contribute to basic understanding of vestibular mechanisms. Research is needed to:

- Characterize at the behavioral level the progression of perceptual and reflex function during development and aging.

- Conduct anatomic and physiologic research to determine the mechanism(s) underlying development of central vestibular pathways, their relation to development of peripheral end-organs and the ontogenetic sequences of connectivity between vestibular neurons and motor and higher sensory centers in the brain.

- Study how membrane and synaptic properties of hair cells and vestibular sensory and motor neurons change during development and aging and examine the roles of neural activity and neurotransmitters in producing those changes at the cellular level.

- Determine the neurotransmitters present in vestibular brain stem nuclei over the course of development, maturation and aging.

Major Clinical Scientific Opportunities

There are six broad high priority areas for clinical vestibular research: prevalence and environmental factors; anatomic, physiologic and molecular bases; diagnostic methods and testing procedures; adaptive mechanisms; and medical and surgical therapy. These opportunities can be summarized as follows:

Prevalence and Environmental Factors

It is important to develop a better understanding of disease prevalence and possible associated environmental factors. Research is needed to:

- Assess the distribution of balance disorders among different sectors of the population (including age, gender, genetic background and geography).

- Identify environmental and occupational hazards that adversely affect balance.

- Carry out a demographic study to evaluate the deleterious effects of prescription and over-the-counter medications which may produce central or peripheral vestibular alterations.

Anatomic, Physiologic and Molecular Bases

A better understanding of anatomic, physiologic and molecular bases of normal and abnormal balance processes is needed.

- Determine modifications of neuronal vestibular pathways in animal and human pathologic specimens with known vestibular dysfunction.
- Analyze the molecular and pharmacologic properties of specific groups of relay neurons in postural and gaze reflex pathways. The development of these properties from embryo to adult vestibular systems should be traced and changes that accompany aging examined.
- Determine the coexistence of multiple neurotransmitters within single vestibular synapses.
- Determine the excitatory and inhibitory neurotransmitters in the vestibular portion of the brain stem nuclei during development, maturation and aging.
- Develop animal models to study the pathophysiology of vestibular diseases.
- Examine structural changes in vestibular pathways in animal and human pathologic specimens with known vestibular dysfunction.
- Investigate the molecular basis of acquired and congenital inner-ear disorders in humans and animal models.
- Study and correlate peripheral and central pathologic abnormalities with biochemical and molecular changes in human subjects with well-studied disease.

Diagnostic Methods and Testing Procedures

Improved tests of balance function, a more standardized method of testing and research on pathology are needed.

- Develop new tests to evaluate otolithic organ and vertical semicircular canal function in humans, including freely moving subjects.
- Develop tests to define the contributions of neck receptors to normal gaze and balance function and to vertigo and imbalance in pathological conditions.
- Develop new tests for vestibular function involving non-invasive recording of neural activity and/or reflex responses elicited by specific

mechanical or electrical stimuli that activate vestibular afferents.

- Develop new and improved methods for the evaluation of posture under static and dynamic conditions.
- Develop standards for the more commonly used diagnostic tests in the vestibular test battery.
- Develop improved psychophysical methods for evaluation of vestibular function in health and disease.
- Develop animal models to study the reliability and validity of new vestibular tests.
- Develop methods to detect immunologic and autoimmune inner-ear disorders and neoplasms for the diagnosis of vestibular system disorders.
- Validate currently accepted diagnoses or new diagnoses based on clinical pathologic correlation.
- Conduct serial (longitudinal) studies of the changes in vestibular tests in patients with well-defined pathologic processes.

Adaptive Mechanisms

Adaptive mechanisms play an important role in normal balance function, compensation for disease and rehabilitation.

- Analyze the molecular and pharmacologic bases of adaptive changes in the vestibular system.
- Investigate the use of pharmacologic agents to modulate changes in adaptive compensation.
- Extend studies of adaptive behavior to consider the conditions of unilateral and bilateral labyrinthectomy in an attempt to understand the response to vestibular damage.
- Determine if there is a critical period for the initiation of vestibular exercises to facilitate recovery following the sudden onset of vestibular loss or dysfunction in humans.
- Determine the optimal characteristics of vestibular stimulation necessary to facilitate recovery in different vestibular disorders.

Medical and Surgical Therapy

Medical and surgical therapy is frequently based on insufficient determination of efficacy. Standardized reporting of results is critical, and the efficacy of treatment should be determined.

- Perform multicenter, prospective, controlled clinical trials which:

  - evaluate medical therapy for vestibular symptoms.
  - evaluate osmotic or renal loop diuretics for the treatment of episodic vertigo.
  - compare medical to surgical ablative therapy in Meniere's disease.

- Study the pathologic effect of vessel loop compression on the vestibular nerve and the effectiveness of vessel loop relocation.

- Study the anatomic, physiologic and pharmacologic central nervous system correlates of neurectomy (partial and total) compared to labyrinthectomy in appropriate animal models.

- Determine the effect of surgical manipulation of the cochlear nerve and the facial nerve intracranially and in the internal auditory canal.

- Determine the effect of the peripheral and central molecular, biochemical and structural changes following various ablation procedures, e.g., labyrinthectomy, and partial and total vestibular neurectomy.

SMELL, TASTE AND TOUCH AND CHEMOSENSORY DISORDERS

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SMELL, TASTE AND TOUCH AND CHEMOSENSORY DISORDERS

Overview

Smell and Taste

The chemical senses (olfaction or the sense of smell and gustation or the sense of taste) detect and identify chemical stimuli in the environment. These stimuli include foods, environmental chemicals and pollutants, hazardous vapors and gases, as well as pleasurable aromas, scents and fragrances. Thus, deficits in these senses present a number of serious problems: they can eliminate the ability to recognize and the motivation to consume nutrients; they can reduce the ability to detect toxicants in the home and workplace; and they can decrease the pleasure derived from meals, the environment and interpersonal interactions. In addition, abnormalities in chemosensory responses frequently accompany and even signal the existence of unhealthy conditions or diseases, including obesity, hypertension, malnutrition, diabetes and some neurodegenerative diseases such as Alzheimer's disease.

Disorders of the chemical senses account for thousands of visits to physicians every year. Patients with chemosensory disorders report both partial and complete olfactory and gustatory losses, distortions of smell and taste, as well as phantom odors and tastes. The most common causes of chemosensory disorders are nasal and paranasal sinus disease, allergic rhinitis, upper respiratory infections and head trauma. A better understanding of these disorders and their causes should provide information which can be applied to strategies for prevention and treatment of chemosensory disorders.

Touch

Touch is an important communicative sense. It provides information about objects in contact with the skin and, through transmitted mechanical disturbances, information about events and objects at a distance. Touch often combines with other senses such as the kinesthetic and vestibular senses to provide information about the position of an individual in space. In combination with the chemical senses, it is an important component in appetitive behavior. Touch is an important communication channel for persons who are blind (Braille), profoundly deaf (vibrotactile aids) or deaf and blind (individuals receive communication by tactile stimulation from an interpreter). Touch plays an essential role in many motor behaviors, such as the chewing and swallowing of food, the control of articulation of speech and the maintenance of balance.

Touch is closely involved with taste. The appreciation of food involves not only stimulation of olfactory and gustatory receptors but also thermal and tactile receptors as well. Loss of touch sensitivity in the oral cavity may thus affect both motor and sensory aspects of eating. Touch has been shown to affect such basic processes as the localization of taste sensations within the oral cavity, and evaluation of the sense of touch may be of diagnostic value in some taste disorders.

Incidence, Prevalence and Costs

Information about the incidence and prevalence of disorders affecting the chemical senses is limited. Historically, the best estimates of prevalence were based on extrapolations from clinical referral data, but they could not be considered valid or reliable. In the late 1970s, the opinion of many experts was that more than two million adults in the United States had a chemosensory disorder.

The earlier, rough estimates on chemosensory disorders were improved in 1987 for the sense of smell following an international population survey conducted by chemosensory scientists with the help of the National Geographic Society. Using a "scratch-and-sniff" format test, the National Geographic Society invited readers of its magazine to identify a series of six odorants and answer several questions about the sense of smell. More than one million people responded. Although this was a nonrandom sample (the readership of the National Geographic Society tends to be drawn from the higher socioeconomic strata), the results are nonetheless noteworthy. Highlights of the survey include the following findings:

- Two of every three respondents reported temporary losses in their sense of smell which were often associated with colds, influenza, sinus conditions and allergic rhinitis.
- Although one-half of the respondents could detect all six test odorants, one percent of the respondents could not smell three or more of the odorants. Nearly all could appreciate the odor of banana, but only one-half could identify it.
- More than one-third of the respondents could not detect the sweat-like odorant. Also, nearly one-third could not detect the musk-like odorant.
- Age factors were important. Overall smell sensitivity begins to decline in the second decade and deteriorates appreciably with age.

An unexplained and disturbing finding of the survey was that a substantial segment of the elderly showed a loss in the ability to detect the foul-smelling mercaptan added as a warning agent to natural gas.

- Consistent with other findings, losses of the sense of smell were associated with smoking.
- Females of all ages identified more odors than did males. The common belief that pregnancy increases sensitivity to odors was not supported by the actual intensity ratings and smell detection tests.

Comparable data are not currently available for taste. However, with the creation of clinical centers for smell and taste disorders, information has begun to accumulate.

Even the limited epidemiologic information available is proving highly valuable as scientists and clinicians try to understand chemosensory disorders and to assess their impact on the population of the United States. Although extensive data are not available, smell and taste disorders have been shown to affect diet. Many individuals with olfactory and gustatory deficits appear to maintain nutritionally adequate diets, but marked changes in body weight do occur in others. Some individuals increase their intake of sweets, salt and spices to derive pleasure from eating, possibly exacerbating chronic health disorders such as obesity and hypertension. Further, losses in the capacity to identify specific odors may interfere with an individual's ability to detect toxic substances and reject spoiled or contaminated foodstuffs.

The psychologic impact of chemosensory losses is another important concern. Reports are anecdotal, but the magnitude of impact varies widely and responses can range from stoicism among some individuals to serious complaints, including suicidal impulses, among others.

The problems associated with chemosensory deficits can be greatly exacerbated when the deficits are combined or associated with chronic illnesses such as cancer, renal failure or liver disease. In such situations, smell and taste disorders can contribute to problems of anorexia and cachexia and thereby place individuals at additional risk for poor nutrition.

Although methods of evaluating chemosensory sensitivity are available, refinements and improvements are needed. For example, a "scratch-and-sniff" test provides an accurate and readily administered, suprathreshold odorant identification test. A quantitative threshold test, in which odorants are dispensed from squeeze bottles, may be refined for use in physicians' offices. That would permit the physician to quantify the loss and monitor changes over time.

Refinements in gustatory sensitivity tests are also under development. For instance, refinements that permit measurements of taste sensitivity over different areas of the tongue are proving useful for detecting and locating gustatory deficits and other forms of neurogenic damage.

The cost of chemosensory disorders cannot be determined with certainty until better epidemiologic data are available. However, daily life costs and the quality of life is adversely affected for those people in the United States with these disorders.

Disorders of touch and other sensations result from neurogenic disorders, psoriasis, thermal and mechanical trauma including frostbite, burns, penetrating wounds and amputations. Disorders of touch are also associated with exposure to vibration in the hand and arm vibration syndrome which may produce an immediate economic impact on persons who work with their hands. The 1989 National Institute for Occupational Safety and Health estimate on occupational exposure to hand and arm vibration indicates that the prevalence for this syndrome for the 1.45 million workers exposed to vibration is 50 percent. Disorders of touch are also associated with trauma to the central nervous system, including stroke, penetrating head wounds or concussion and congenital malformation or perinatal anoxia, and other injuries during gestation or at birth. Estimates of the prevalence of these disorders vary, but the number probably ranges from three to five percent of the population.

Recent Accomplishments

Smell and Taste

Stimulus Characterization and Detection and Signal Transmission

The olfactory receptor neurons are located in the olfactory neuroepithelium in the roof of the nose. The axons (fibers) of these neurons enter the skull and synapse (make contact with) other neurons in the olfactory bulb. The taste receptor cells form taste buds on the tongue, palate, pharynx (throat) and larynx (voice box). Several nerves subserve taste and carry information from the taste buds to the brain stem.

Studies of perireceptor events in smell and taste have revealed the presence of binding proteins that may act to deliver or remove lipid-soluble stimulus molecules. The presence of enzymes to metabolize xenobiotic (foreign) molecules suggests a mechanism to inactivate stimulus ligands (binding molecules).

The application of contemporary cellular, molecular, anatomic and electrophysiologic methods and the increased use of various unicellular and invertebrate species have resulted in substantial advances in understanding the basic mechanisms of smell and taste. More information is available about stimulus access and elimination, putative receptor identification, transduction mechanisms and cellular interactions.

Advances in molecular biology include the demonstration that olfactory receptor neurons express novel members of the large family of genes that encode the olfactory receptor molecules. Olfactory receptor molecules are large proteins that weave from the inner to the outer surface of the cell membrane seven times and are called seven-transmembrane domain proteins. In addition, components of transduction pathways including G-proteins, adenylate cyclase and cyclic nucleotide-gated channels have been cloned. The second messenger, inositol trisphosphate, has also been implicated in olfaction. Studies using transgenic mice have demonstrated the ability to direct the expression of exogenous genes in olfactory neurons thereby indicating the existence of chemically repetitious segments of genes known as genetic motifs which convey specificity to receptor molecules. Related in vitro studies have begun to characterize the molecular components responsible for olfactory transduction. Electrophysiological and optical recording techniques have been applied to chemosensory systems, revealing that a variety of transduction mechanisms function in olfaction and gustation. Cyclic nucleotide- and inositol trisphosphate-gated ion channels appear to participate in olfactory transduction. In gustation, both direct interaction with apically located ion channels and receptor-activated, second-messenger systems have been demonstrated. A gustatory-specific G-protein, gustducin, has been cloned, providing an entree to molecular dissection of gustatory transduction. Efforts to culture olfactory receptor cells and develop clonal cell lines, while at an early stage, promise to provide new opportunities for the study of chemosensory transduction and the identification of the factors regulating the development and maintenance of receptor cells.

Understanding the development of the olfactory system has been advanced by several recent accomplishments using in vivo and in vitro approaches. Cell adhesion molecules and trophic factors that may be important for the development of olfactory glomeruli (located in the olfactory bulbs of the brain) have been identified. Some of these molecules appear to be used by several important animal groups, including insects and mammals, underscoring the value of accessible animals as basic research models of mammalian chemosensory function. Similarly, recent findings indicate that glial cells play an important role in the establishment of olfactory glomeruli in insects and mammals. These cells and other nonneuronal cells appear to be important for the normal development and regeneration of mammalian olfactory receptor cells.

The importance of olfactory receptor cell axons in the development of the olfactory bulb has been reinforced by recent studies of partial removal of these axons to the olfactory bulb. Quantitative studies of the frog olfactory bulb demonstrated that the number of olfactory axons is proportional to the number of olfactory bulb neurons. In the rat, olfactory axons regulate cell cycle kinetics in the developing telencephalon (part of the brain from which the cerebral hemispheres develop). Olfactory axons appear to regulate transmitter gene expression in the developing and adult olfactory bulb of the rat. Experiments in mice in which one side of the nose is closed suggest that loss of afferent innervation may not be the only mechanism for producing defects in olfactory-bulb development; sensory stimulation or afferent activity also may play an important role in bulb development. In the future, it will be important to unravel the cellular and molecular mechanisms controlling neuron-neuron and neuron-glial interactions, as well as to define the role of environmental stimulation in olfactory-system development.

Studies in vivo and in vitro have shown that various molecules are transiently expressed in olfactory receptor cells during differentiation and maturation. Full maturation and neuronal survival of olfactory receptor cells are dependent upon continued axonal contact with a suitable target like the olfactory bulb. In addition, there is increasing evidence that the life cycle of olfactory receptor cells is controlled more by environmental influences than by intrinsic cellular mechanisms regulating cell turnover. New studies are needed to identify the relevant molecules, genes and cells controlling these interactions.

Although the basic anatomy of chemosensory epithelia and their primary and secondary brain regions has been characterized, there is a further need to understand the organization of chemosensory connections to the brain and how their brain regions actually process chemosensory information. In olfaction, recent experiments confirm and amplify earlier observations that a receptor cell's location in the olfactory neuroepithelium does not predict precisely where it connects to the olfactory bulb. Consequently, the organization of connections between the olfactory neuroepithelium and the olfactory bulb differs from the point-to-point design characteristic of touch projections from the skin to the brain. This realization will prompt investigators to evaluate functional features such as odorant class or receptor cell responses as a basis for the arrangement of olfactory projections to the brain.

Recent experiments have demonstrated that odors cause activity in the olfactory nerves that stimulates the expression of immediate early genes in local areas of the olfactory bulb. The application of voltage-sensitive dyes and optical recording techniques to the study of the chemical senses has demonstrated their utility in identifying populations of neurons that respond to specific sensory cues. Corticotropin releasing factor has been discovered to be a transmitter in olfactory-bulb mitral cells, the major class of bulb-output neurons in many mammals. Cholecystokinin is a peptide transmitter in tufted cells, the other major class of bulb-output neurons. The functions of these potent excitatory neuropeptides should be determined. Olfactory bulb activity is greatly influenced by other brain systems, especially aminergic and cholinergic systems of the forebrain, which serve to modulate the responsiveness to specific sensory inputs.

Recent advances in in vitro slice recording techniques and immunocytochemistry in the solitary (gustatory) nucleus have begun to explore functional circuitry and synaptic mechanisms in sensory processing. The development of in vitro preparations for studies of the olfactory bulb is badly needed. Using information from in vitro studies of piriform cortex, computational models are being developed to explore the mechanisms involved in the discrimination and categorization of sensory cues, learning and memory. Computational models for the olfactory bulb are needed.

Recent developments in the field of neurobiology offer significant opportunities to advance the understanding of the chemosensory and touch systems. There has been an explosion of information on neurotrophic factors and the important, newly discovered developmental and functional roles of glial cells. Such information suggests that trophic factors and neuron-glia communication are critical to the development, phenotypic differentiation and viability of diverse populations of forebrain neurons. That is of particular interest with regard to the olfactory system because the agents regulating the ingrowth and replacement of olfactory nerve innervation of the olfactory bulb and the mechanisms through which olfactory nerve innervation shape the anatomical and biochemical development of target structures have yet to be identified. In related studies, progress has been made in understanding the mechanisms of neuronal cell death in a variety of contexts including normal development, response to prolonged exposure to excitatory neurotransmitters and following withdrawal of trophic support. This work in invertebrates has identified genes leading to either programmed cell death or to survival through development. Studies of mammalian neurons have indicated there are general mechanisms of cell death and protection from insult. Hypotheses deriving from work in this area might be tested in studies of olfactory receptor cells that exhibit a brief lifespan.

There has been substantial progress in the development of techniques for studying organized brain regions in vitro in the form of either acute slice preparations (viability is five to ten hours) or organotypic slice cultures (viability is approximately one month). Such cultures have provided new opportunities to study the development, electrophysiologic properties, neurochemical phenotypes and neural network properties of brain circuits in culture. Preparations of these sorts offer unprecedented new opportunities for studying central chemosensory structures.

The sense of smell appears to be essential for suckling in some species of mammals. Flavors consumed by the mother can be transmitted in human milk and have been shown to modulate suckling. Her odors are detected and recognized by her infant. Taste may also play a major role in suckling. At birth, humans, and many other mammals have numerous taste buds, some of which increase their sodium responsiveness over a period of weeks. In contrast, some rodent species living in arid environments show no developmental increase in sodium responsiveness but rather have strong sodium responses shortly after birth. This work suggests that adult and developmental responses are closely related to life history patterns.

The salivary environment of the oral cavity is critical to some oral sensory experiences. Astringency may arise from hydrogen bonding of tannin molecules to salivary proteins. This hypothesis is supported by the production of many proline-rich proteins by the salivary glands. Such proteins have a disrupted helical structure that exposes groups susceptible to hydrogen binding by tannin. Some animals appear to increase production of such proteins in response to a tannin-rich diet, which possibly produces digestive distress.

Prolonged inhibition has recently been demonstrated in frog and rat taste buds. Such peripheral inhibitory and modulatory influences should be further characterized. In development, fungiform papillae (tongue structures that house taste buds) appear to arise in advance of innervation. However, taste buds themselves are neurally induced during development. Without early innervation, the gustatory epithelium never gains the capacity to support taste buds, even when it is later innervated. Innervation controls not only the formation of taste buds but also the structural appearance and keratin expression of the cells in and around taste buds.

Other forms of plasticity are also observed in the taste system. For example, prenatal sodium deprivation delays the normal development of physiological and behavioral responses to salt. Also, projections to the solitary nucleus in the brain stem can be modified by peripheral denervation or salt deprivation. Apparently, both taste buds and central projections have a greater plasticity than heretofore appreciated.

Nasal, Oral and Trigeminal Chemoreception

Stimulation by chemical stimuli in the oral and nasal cavities involves not only the olfactory and gustatory nerves but also the trigeminal nerves. Recent research in psychophysics has characterized the nature of responses to irritative compounds. Oral trigeminal stimuli include some important food constituents. Nasal trigeminal stimuli include volatile organic compounds present in the industrial workplace and in indoor commercial and residential environments where they can play a role in conditions such as sick building syndrome. Oral trigeminal responses depend upon stimulus, temperature, concentration, duration and area exposed. Capsaicin, a pepper component, can desensitize the oral cavity, both in short-term and chronic (dietary) exposure. Irritants may impair taste sensitivity and increase salivary flow. Opportunities exist for further characterization of oral, nasal and trigeminal chemoreception and its interactions with taste, salivary flow and salivary composition.

Chemosensory Disorders

The establishment of the clinical centers for smell and taste has increased the integration of basic scientists and clinicians studying chemosensory function. There is increased information about the clinical characteristics of individuals with chemosensory disorders resulting from upper respiratory infection and head trauma. In particular, strategies for diagnosis and management of chemosensory disorders have emerged. For example, corticosteroids and surgery have been used effectively to treat nasal and paranasal sinus disease and improve olfactory function. The clinical centers have assembled special patient populations with specific chemosensory disorders, such as parosmia and dysgeusia, that can be used to test new hypotheses about the causes and management of chemosensory dysfunction.

Research with special populations of patients has begun to differentiate peripheral from central loci of chemosensory dysfunction. Patients with head injuries exhibit deficits in olfactory quality discrimination that correlate with localized cortical lesions as seen with computed tomography and magnetic resonance imaging. Individuals with temporal lobe epilepsy show deficits in quality discrimination over and above losses in absolute sensitivity. Unilateral resection of the temporal lobe exacerbates discriminative deficits. Individuals with Alzheimer's disease show impairment in a variety of olfactory-mediated tasks. Performance on a battery of tasks implies both peripheral and central impairment. Increased attention has been focused on the extent of parosmia and dysgeusia, their profound effects on a person's life satisfaction and well-being, and the difficulties associated with their diagnosis and management.

Perceptible olfactory losses have proven to be more common than perceptible taste losses. For this reason, people who self-refer to smell and taste clinics usually have olfactory losses. The primary causes of olfactory loss are head trauma, viral infection, allergic rhinitis and nasal and paranasal sinus disease. Some individuals also tend to manifest localized taste losses of which they are unaware. When one area of the tongue is damaged, other areas produce sensations that are more intense, thereby maintaining a relative constancy of taste experience. Disinhibition of taste buds is an explanation that could be tested.

The diagnosis of hypogeusia has remained elusive. Although taste bud distribution is related to taste perception, studies based on the use of injected local anesthetics have demonstrated that whole mouth testing does not accurately describe hypogeusia. Taste function may be locally impaired on the tongue. Tests have been developed that use stimuli representing each of the four taste qualities (sweet, salty, sour and bitter), and testing can be accomplished for regions of the tongue and palate.

There are large variations in the number and density of taste buds among human subjects. Some variation in human, taste-intensity perception is associated with demonstrated differences in taste bud distribution. This finding suggests that some conditions characterized by diminished taste sensitivity may result from combined effects of taste bud dysfunction and low numbers of taste buds.

Videomicroscopy can be used as a noninvasive method for the quantification of fungiform papillae taste buds in humans. Previously, only surgical biopsy (or postmortem examination) could be used to quantify human taste buds. Videomicroscopy, in association with computer-based image processing, provides a method for the noninvasive quantification of taste buds in humans.

Studies have shown that the smell and taste world of the human infant is varied and rich. Premature infants can detect and respond to taste stimuli. Mother-infant attachments are affected by body odors and flavors experienced by the infant in its mother's milk. These experiences may alter the infant's nursing behavior and perhaps subsequent nutritional choices. Although it is not yet known whether the affective responses to some odors have innate components, it has been shown that by three to four years of age, children exhibit adult-like, odor preferences and aversions.

During the last decade, remarkable progress has been made in establishing the nature of the changes that occur in the chemical senses with age. Age takes a much heavier toll on olfaction than on gustation. Some taste qualities are more affected by aging than others. This finding may permit the development of food products tailored for the elderly as well as other individuals with reduced chemosensory abilities. Food odors can be artificially intensified safely. Since many elderly individuals cannot smell the mercaptan added as a warning agent to natural gas, the search for a level, blend or alternative has real urgency.

Inhaled organic compounds such as menthol and ginger, are perceived as odor and nasal pungency. The pungency of compounds often determines limits on exposure in occupational settings. Studies with normosmic (normal sense of smell) and anosmic (absence of sense of smell) persons have made it possible to specify thresholds for odor and pungency separately and to explore the physicochemical determinants of each sensory attribute. Molecules differ in the increase in concentration required for detecting an odor and experiencing pungency. Pungency for nonreactive compounds appears in general to occur at approximately equal thermodynamic activity. Such a rule implies a relatively nonspecific receptor mechanism and offers predictions regarding untested molecules. In some cases, however, irritation may be mediated by a specific receptor, such as the capsaicin receptor, in taste. Nasal pungency and eye irritation seem to have very similar thresholds. These results have relevance to the basic mechanisms of chemoreception of irritants and to the management or avoidance of exposure in occupational and other indoor settings.

Studies in individuals with a normal sense of smell and in those with brain lesions suggest that the right hemisphere plays a more important role than the left hemisphere in central processing of odor quality.

Hypertension is one of the most common chronic diseases in the United States. It has a high prevalence, particularly in African Americans. Most investigators agree that excess salt intake plays a role in the disease, although exactly what role it plays remains controversial. In rodent studies, substantial evidence has been obtained linking the salt intake of expectant and lactating mothers to the salt intake and blood pressures of their offspring. Whether such associations exist in the human population requires additional study.

Studies in animal models with the sodium-channel blocker, amiloride, indicate that salt taste reception mechanisms involve, in part, passive sodium transport. Recent psychophysical studies encourage the use of amiloride as a pharmacologic tool for assessing salt taste in humans.

Inflammatory nasal and paranasal sinus diseases such as allergic rhinitis and chronic sinusitis are major health concerns of the American population. These processes interfere with the ability of some individuals to detect odors. Although the mechanism for this loss of the sense of smell is not fully understood, appropriate medical and surgical management often improves olfactory function.

Biopsy and scanning electron microscopy have expanded understanding of normal and abnormal morphologic characteristics of human olfactory neuroepithelium.

The nature of olfactory dysfunction in Alzheimer's disease is becoming better understood. Impairment of olfactory sensitivity is related to the degree of dementia. Older people with Down syndrome show neuropathologic changes similar to that of patients with Alzheimer's disease. Individuals with Down syndrome have been shown to have deficits in olfactory function.

Important findings have been made regarding chemosensory dysfunction in Sjögren syndrome, an autoimmune disorder. Overall, people with Sjögren syndrome manifest a decrease in their ability to identify odors: some patients are markedly impaired, while others are less so. Taste deficits associated with Sjögren syndrome are much less marked than olfactory deficits observed in the same individuals. Detection of weak taste stimuli is impaired, but appreciation of taste intensity is intact. Moreover, chemosensory dysfunction in Sjögren syndrome is unrelated to disease severity.

Touch

During the past decade, advances have been made in using the skin to aid individuals with communication disorders, such as vibrotactile aids for persons who are deaf, blind, or deaf and blind. There has been progress in understanding the most effective ways individuals with disabilities may make use of such aids. Multichannel vibrotactile aids, for example, have shown considerable promise in improving speechreading performance. These devices may be particularly useful in patients for whom cochlear implants or other surgical procedures are contraindicated. Devices to convert printed characters directly to tactual patterns that can be read by persons who are blind continue to improve, as have tactual displays for use in mobility training of people who are blind or deaf and blind.

Recent progress in understanding cutaneous sensitivity has resulted from work in various areas. These include neurophysiology, experimental psychology, neuroanatomy, rehabilitative specialties, biomechanics, engineering, robotics and teleoperator systems.

Of particular importance in understanding the somatosensory system is the long and close coordination of psychophysical studies of human subjects and neurophysiological studies of nonhuman subjects. Microneurographic studies have examined peripheral nerve fiber responses recorded from awake human subjects. The subjects can report the sensations resulting from mechanical stimulation, and the results can be compared with simultaneously recorded neural responses. Studies with brief, repetitive and prolonged stimuli have suggested how temporal and spatial patterns, such as Braille, are encoded for processing by the nervous system. In conjunction with other psychophysical results from human subjects, these microneurographic results have greatly clarified the nature of encoding by peripheral mechanoreceptor afferents. Also, sophisticated psychophysical techniques used with nonhuman primates have shown changes in the animal's sensitivity to mechanical stimulation and corresponding changes in the central nervous system as a function of specific kinds of tactile experience.

Basic studies of tactile sensitivity have guided the development of sensory aids for people with disabilities, such as reading aids for the blind. Conversely, the use of these aids has led to new discoveries about some little-known sensory capabilities of the skin, and these aids are being used by scientists to answer basic questions about the sense of touch.

There is an increased appreciation of the role of touch combined with kinesthetic information in identifying objects. Progress has also been made in developing classification schemes for the hand movements performed to extract certain kinds of haptic (tactile) information and in the development of displays that deliver both haptic and kinesthetic information. Related to these efforts is the work on robotics and teleoperator systems that has led to a greater understanding of the role of touch and kinesthetic information in controlling hand and limb position. New studies may prove important in the development of feedback for prosthetic limbs.

Food taste components, like polyphenols, acids and some salts, cause astringent sensations. These stimuli make mouth tissues feel dry and rough and cause drawing or puckering sensations. Psychophysical studies have characterized astringent reactions with regard to temporal properties, effects of different flavor molecules and interactions in mixtures. Although the stimuli for astringent sensations are chemical, their effects are largely tactile. Because movements are required for drying and roughing sensations to be fully appreciated, the study of astringency lends itself to methodologies that allow an active perceiver as in human psychophysical approaches. Astringent effects may derive from changes in the composition of salivary constituents that lubricate the oral surfaces. The importance of the interplay among saliva, chemical stimuli and oral tactile sensations is underscored by oral sensations such as astringency.

Program Goals

Basic Science Goals

Stimulus Characterization and Detection and Signal Transmission

Cellular, Molecular and Genetic Bases of Olfactory Reception

The cellular and molecular mechanisms used by chemosensory systems for stimulus detection and transduction are similar to those used by other peripheral and central neural systems. This provides a conceptual framework to apply contemporary techniques of molecular biology and cell biophysics to study chemosensory receptor mechanisms. The strength of these approaches is already evident. Examples that illustrate this fact include: the identification of the gene for Kallmann syndrome; the cloning of olfactory- and gustatory-specific G-proteins; the demonstration of a large group of novel putative olfactory receptor molecules having seven-transmembrane domains; the characterization of a novel cyclic nucleotide-gated and an inositol trisphosphate-gated channel; the application of transgenic animal models to study the mechanisms regulating chemosensory gene expression; and facilitation of the creation of clonal cell lines.

To stimulate olfactory receptors, odorant molecules must be transported by airflow to the olfactory cleft where they settle on the surface of the neuroepithelium, diffuse through the mucus to the receptor cells, interact with receptors, and engage metabolic and stimulus-eliminating mechanisms. Although these processes are not well understood, their disruption may be the basis for some olfactory disorders. The principles of fluid mechanics and mass transfer should be applied to studies of the transport of odorant molecules to receptor cells. Particular attention should be given to how changes in nasal morphology, sniffing characteristics, secretory processes and metabolism of xenobiotics might alter odorant transport.

Investigations that will lead to the knowledge necessary to understand and treat individuals with chemosensory disorders will likely use single cell isolation, patch clamp and optical recording techniques, strains of transgenic and mutant animals, molecular and genetic probes for analysis of function, chromosomal mapping, in situ hybridization and immunocytochemical techniques for the localization of specific molecules as well as transformed or engineered cell lines to study the basic biology of signal detection and information processing.

Cell Membrane, Synaptic Transmission and Neural Network Mechanisms in Chemosensory Function

Taste buds and olfactory neurons are located at the interface between the external, chemical world and the internal milieu of the organism. Chemical stimuli must be detected and transduced into electric signals that elicit neurotransmitter release and neural impulses for transfer of information to the central olfactory and gustatory pathways of the brain. Even before the chemical stimuli reach the receptor cell surface, they must traverse aqueous media that contain specialized proteins that may facilitate the transport and detection of the substances. Chemosensory stimuli are diverse, necessitating a variety of receptor molecules and mechanisms for their detection and transduction. Although olfactory receptor cells send their information directly to the brain, taste receptor cells are organized into special end organs in which processing of taste information may occur prior to transmission toward the brain. Despite recent progress in understanding neurotransmission in other sensory systems, investigators have not yet identified the neurotransmitter(s) for olfactory and gustatory receptors.

Advances in neuroscience techniques permit the investigation of many of the basic principles underlying the phenomena involved in chemosensory transduction and transmission. Such techniques include molecular cloning, single cell isolation and recording, formation of new genetic and transgenic strains of laboratory animals, generation of clonal cell lines that differentiate into functional sensory cells, optical recording, and specialized immunologic and genetic probes. These techniques promise to provide new insights into the fundamental processes involved in the detection and transmission of chemosensory signals.

Sensory Coding in Chemosensory Processing

For the senses of smell and taste, the quality of the stimulus molecule detected by the receptors is encoded in the information transmitted to the brain. This information is processed by complex networks of neurons lying within sensory areas of the brain. Although some of the patterns of anatomic connections in these networks are known, the functional anatomy of sensory coding is poorly understood.

Olfactory receptors make divergent projections to the brain. Rather than a spatial point-to-point map of the sensory epithelium as found in the sense of touch, recent studies raise the possibility of a functional map of odors within the brain. It is clear that additional data are needed to characterize the basis of olfactory projections. The projections of taste buds reflect the projections of the relevant cranial nerves. Taste axons of the facial nerve can converge from different parts of the oral cavity to common sites within the brain stem. Modern measures of functional arousal, such as immediate early gene expression, can clarify whether different classes of taste solutions, like sugars, map to specific subareas in taste regions. To understand sensory processing mechanisms, the neurotransmitters and neuromodulators in these taste regions will also need to be identified.

Advances in molecular, biophysical, cellular and tissue culture techniques permit the functional analysis of neuronal elements in the processing system. Functional and structural analysis of central smell and taste networks should yield insights into the neural codes underlying smell and taste perception. Modern computer technology makes modeling these networks possible.

New opportunities arise from the conjunction of molecular and developmental biology. Recent advances have been made in characterizing morphogenetic steps in the development of olfactory receptor neurons and taste buds. Similarly, progress has occurred in understanding transcription, signal transduction and trophic factors in these systems. The development, plasticity and aging of chemosensory systems should be examined using the molecular, cellular and networking principles identified from a wide variety of other biologic systems.

Since both sodium deprivation and damage to taste nerves modify the anatomic pattern of sensory projections into the solitary nucleus, taste areas in the brain may be modified during development. Consequently, it is important to evaluate the vulnerability of chemosensory development to nutrient deficiencies, maternal diabetes or alcoholism and other disorders that alter the prenatal environment. Observations that selective odor exposure leads to "disuse atrophy" of the olfactory system should be further explored.

Integrative and Network Functions of Central Olfactory, Gustatory and Tactile Structures

Smell, taste and tactile information is conveyed to distinct, parallel neuron systems that mediate different functions such as swallowing, digestion, reproduction, endocrine function, learning and memory and social behavior. Understanding of the basic neural circuits underlying the integration of chemosensory inputs into organized behaviors lags far behind that of other sensory systems. Research should be directed toward determining the specific brain areas involved in these functions, as well as in higher processes such as sensory discrimination, stimulus identification and learning. Research also should be directed toward identifying the mechanisms by which processing in these neural networks is integrated with other functional systems in the brain. The development and use of in vitro tissue slice preparations to isolate and pinpoint specific cellular networks and transmitter functions are badly needed as these approaches have led to rapid progress in other neural systems. In addition, it will be important to conduct experiments employing chronic neurophysiologic recordings, voltage-sensitive dye recording, biologically realistic, computational models and activity-stimulated changes in gene expression. Research on the detailed circuitry and neurotransmitters mediating chemosensory reflexes, such as coughing and gagging, may shed light on the possible involvement of these reflexes in pathophysiologic disorders such as sudden infant death syndrome. Studies of the nature of cognitive impairments in human disorders involving degeneration of neurons (e.g., Alzheimer's disease and epilepsy) in structures of the chemosensory or tactile systems should provide insights into the functional organization of cognitive processing in man.

An important approach to understanding sensory processes has been the use of combined psychophysical and neurophysiological studies. In such studies on touch, psychophysical measurements are obtained, generally from human subjects and the same stimulus conditions are used to examine neurophysiologic responses, typically in monkeys. In a closer conjunction of psychology and physiology, studies have examined taste and touch peripheral nerve fiber responses in awake human subjects who may simultaneously report their sensations.

Building on this foundation, investigators are recording from central projection areas, primarily in the monkey somatosensory cortex, to examine how spatial information is encoded and transformed as it is distributed from primary projection sites through association areas. Psychophysical studies of spatial pattern perception in human subjects are providing an understanding of how such patterns are processed and how sequentially presented patterns affect one another. Continuing work in this area offers considerable promise of increased understanding of tactile processing in particular as well as processing in other modalities, such as how spatial information is encoded visually. Coordination of psychophysical and neurophysiological approaches should be extended to the chemosensory systems. Investigations of somatotopic organization in cortical and subcortical areas have shown that these areas possess a remarkable degree of plasticity. The results not only suggest an important role for experience in determining central nervous system organization but also offer insights into possible recovery from peripheral and central nervous system injuries. Similar structure-function studies of plasticity in chemosensory systems are needed. Advances of this kind underscore the importance of parallel measures of neurophysiologic and behavioral function.

Fabrication of computer-based tactile stimulators is critical for developing tactile aids for persons who have sensory disabilities, in conducting controlled clinical evaluations and in gaining a basic understanding of tactile sensitivity. Knowledge has developed to the point that enough is known about tactile sensitivity to specify the parameters of an ideal tactile stimulator, its frequency response, the amplitudes needed and the spacing between contact points. Newly developed tactile stimulators may enable basic scientists to investigate the psychophysical and neurophysiological capabilities of the skin in human and nonhuman subjects. Tactile stimulators may also enable clinicians to measure capabilities as well as sensory deficits, and their development may encourage prosthetics specialists to design devices and procedures that will assist individuals with disabilities.

Central Mechanisms

Olfactory mixture recognition is poorly understood. Studies on identification of odor components in multicomponent mixtures have emphasized the difficulty of this task. This outcome contrasts with everyday experience, such as recognition of off-odors or taints in food, smoke or gas odors and many other common experiences involving the identification of individual odorant characteristics among a background of other odorants. Addiction and habituation to odors may be involved in this ability although relatively little is known about these processes. It is unclear why different chemical mixtures are classified as having the same general odor. The volatile composition of natural products can vary over a wide range and yet still be recognized as a particular food. How the olfactory system achieves this categorization in the face of a changing stimulus array is unclear. Humans can become trained to be good analytical smellers and to develop constancy in perceptual classification. Thus, odor learning probably contributes substantially to odor perception, particularly of complex stimulus mixtures.

Within the brain the processing of taste, smell and touch information is performed by complex neural networks that include local circuits and circuits engaging other brain systems. The functional anatomy of the network mechanisms that perform central processing is poorly understood. Recent findings in olfaction support the presence of chemotopic representation encompassing multiple neuronal populations in the olfactory bulb, but the spatial representation of olfactory qualities and intensity remains unknown. There is little information on the mapping of olfactory or gustatory information in other brain areas. A major goal of future research is to continue efforts to explore chemotopic representation in other chemosensory centers. Future research also should be directed toward determining the involvement of particular brain areas in processes such as sensory discrimination, stimulus identification, learning and memory. Moreover, studies should be directed toward identifying the mechanisms through which processing in these systems is integrated with other functional systems in the brain. Studies of the nature of cognitive impairments in disorders involving degeneration of neurons in structures of the chemosensory and tactile systems should provide insights into the functional organization of cognitive processing.

Several lines of evidence point to the importance of cognitive mechanisms in the experience of touch. In the identification of spatially separated, tactile patterns, attention mechanisms have been shown to operate much in the same way as they operate with spatially separated, visual stimuli. Little is known of the role of attention in smell and taste perception. Considerable work has been done on the roles that learning and memory play in identifying tactile patterns, but there is little understanding of the roles of learning and memory in olfaction and gustation. Additional studies of these mechanisms are needed to characterize more fully the experience of chemosensation and touch.

Plasticity, Development, Replacement, Regeneration and Aging

The olfactory system offers special opportunities for understanding the fundamental mechanisms of neural development, replacement, regeneration, plasticity and aging because of the unique replacement properties of the neurons in this system. The olfactory neurons can be replaced following chemically or mechanically induced trauma. This distinctive feature of the olfactory neurons is possible because basal cells in the olfactory neuroepithelium retain the ability to divide and differentiate into olfactory neurons. The process can take place even when the olfactory neuroepithelium is transplanted to other body regions, making the olfactory system an excellent model system for use in developing treatments that involve neuronal replacement. Another important feature of neuronal plasticity in new olfactory neurons is the ability of the olfactory axons to grow into the central nervous system (CNS) and form synaptic contacts. It is important to understand the mechanisms that permit olfactory axon growth into the mature CNS. In particular, identifying interactions of growing axons with extracellular matrix molecules and with trophic factors of glial origin might suggest ideal growth environments that can be exploited to facilitate axonal growth and recovery in other neural systems following damage. These studies should also help identify signals important for target recognition and synapse replacement.

When olfactory axons are transected, the olfactory neurons die and are replaced by immature olfactory neurons. These new olfactory neurons are thought to remain immature and be short-lived if existing, mature olfactory neurons remain healthy and in contact with the olfactory bulb. Identification of the signaling mechanisms that suppress maturation of immature olfactory neurons or that facilitate development of immature olfactory neurons when mature olfactory neurons die may lead to a greater understanding of cell death as well as neuronal development. Identification of factors that stimulate death of immature olfactory neurons could suggest new factors to look for in diseases involving neuronal degeneration; appropriate treatments might include the use of drugs to block transmission of the "death signal." In addition, treatment with factors that facilitate development of immature olfactory neurons may stimulate neuronal growth in brain regions devastated by trauma or by Parkinson's, Huntington's or Alzheimer's disease.

Due to their unique replacement abilities throughout life, the olfactory neurons also have a remarkable trophic influence in the developing brain. Preventing olfactory axons from contacting the developing rostal brain results in a failure of the olfactory bulb to form. Identification of the relevant factor or factors secreted by or present on the olfactory axons, as well as the genes involved in producing these factors, may increase our understanding of the causes of certain birth defects and suggest potentially valuable methods of treatment.

As with olfaction, gustatory cells have special properties that contribute to plasticity in the gustatory system. Taste cells renew themselves throughout life in a process of continuous turnover that necessitates remodeling of connections with the afferent taste nerve fibers. The continued renewal of taste receptor cells may underlie some of the changing responses, preferences and aversions for specific foods and flavors observed in the gustatory system from birth and throughout the lifespan.

Taste buds degenerate if their peripheral innervation is removed, but they regenerate upon reinnervation. Taste buds also are susceptible to cycles of degeneration and regeneration associated with repeated radiation and chemotherapy treatments. Thus, the taste system offers unique and as yet underutilized opportunities to study the trophic factors and neural mechanisms that maintain receptor systems that are renewed throughout life. Investigations of basic mechanisms that underlie taste cell turnover and regenerative properties should be pursued and compared with analogous properties in other neural systems. Development of tissue culture systems will contribute to knowledge about these mechanisms, as well as provide models for basic biochemical and electrophysiologic studies of taste reception. Since taste cells are continuously replaced, it is possible that brain networks undergo corresponding adjustments. Little is known, however, about central correlates of peripheral turnover and replacement. Characterization of central plasticity in the taste system is an important goal for future research.

Interaction Among Sensory Systems

Organisms seek sensory experience. This is especially true in the tactile senses, in which the hand or mouth both manipulates and senses objects. It is also a factor in odor perception (seeking an off-flavor in a food, detecting a smoke odor where there may be a fire, or checking the spice level in a new recipe). Active sniffing or chewing may produce sensations different from those derived from odors passively blown into the nose. The exploration involved in nipple-seeking by nursing newborns may involve both olfactory and tactile feedback. In astringency, chemically induced sensations of drying and roughing in the oral cavity may require purposeful mouth movements so that the tongue makes contact with other oral tissues. Food flavor perception may depend upon effective mastication and strategies for bolus preparation. A goal for chemosensory and tactile research should be the study of active perception and purposeful sensation seeking.

Astringent reactions are examples of chemically induced tactile sensations which cause the oral cavity to feel rough and dry and create tightening sensations in the lips and cheeks. Many food flavor components (acids, tannins) and other chemical stimuli (ethanol and aluminum salts) cause such sensations. Although there has been some recent psychophysical characterization of astringent sensations, the mechanisms underlying the interaction of astringent stimuli, salivary constituents and sensory receptors are largely unknown. Future research should be directed toward understanding the interactions of salivary flow, salivary composition, taste sensations and tactile sensations derived from chemical stimulation.

It is obvious that the human experience of the world is not neatly separated into isolated sensory channels as so often appears from laboratory investigations. Contact with objects generates pressure sensations often accompanied by either warmth or cold, or possibly itch or pain. One example of such interaction is a temperature-touch illusion in which a thermal stimulus is perceived to be not at the location at which it is presented but at the location of a pressure stimulus applied to another location. Investigations of these other dimensions of touch should be pursued not only for what they can reveal about the dimensions themselves (for example, studies of cutaneous pain and itch are of obvious importance in therapeutic interventions) but also for what they can reveal about interrelations of the encoding mechanisms of the central nervous system.

One obvious place for complex interaction among the senses is in the oral cavity. Appreciation of food is dependent on the integration of simultaneous smell, taste, touch, temperature and trigeminal signals. Evidence of this kind of interaction is found in the spatial illusion in which the localization of taste is altered by presentation of a tactile stimulus, a counterpart to the temperature-touch illusion noted above. Studies in this field are important for understanding the factors that determine the palatability of food and the detection of an individual's sensory deficits, as well as for understanding normal interactions among the senses.

The perception of flavor involves interactions among smell, taste and trigeminal sensations. Consumers may not readily distinguish inputs from these separate modalities in usual eating or drinking. Psychophysical characterization of smell and taste mixtures has shown approximate additive combination and little evidence for interactions between the two modalities. The literature on food flavor, on the other hand, is replete with interactions between smell and taste perception of volatile flavor molecules. There are no circuits linking the olfactory bulb and brain stem which are the initial central nervous system sites of smell and taste processing, but there are circuits linking higher order olfactory and gustatory structures. Future research should investigate the integration of smell and taste anatomic structures that might play a role in flavor perception or in motivation.

Important goals are as follows:

- Map, identify, clone, and characterize the genes involved in signal detection and processing in chemosensory systems.
- Characterize the cell membrane and neural network mechanisms for detection, processing and synaptic transmission in smell, taste and touch.
- Identify the neural substrates and neurotransmitters for sensory coding at all levels of the chemosensory systems and touch.
- Characterize the neural network circuits mediating perception,

learning and cognitive functions in these senses.

- Identify and characterize the molecular and cellular interactions regulating development, plasticity and senescence in the smell, taste and touch systems.
- Elucidate the mechanisms underlying the unique capacity for cell replacement and functional system regeneration in chemosensory systems.
- Characterize the interactions and functional integration among smell, taste and touch sensory systems.
- Characterize the integrative function of central smell, taste and somatosensory structures for reflexes, perception, learning and higher cognitive processes.

Clinical Science Goals

Epidemiology of Smell, Taste and Touch Disorders

There is a need to assess the incidence, prevalence and risk factors of smell,taste and touch disorders in the United States population. A major national study is required to develop these data, with special attention being given to etiologic, geographic and occupational factors, aging and dementia, gender differences, environmental exposure and genetic and socioeconomic factors.

Development of New Diagnostic Techniques

A major problem associated with the characterization of chemosensory disorders is the lack of definitive diagnostic techniques. Psychophysical tests that not only identify individuals who have a chemosensory loss or impairment but also indicate the probable cause of that loss or impairment, are critically needed. In conjunction with such chemosensory testing, tactile sensitivity measurements in the oral and nasal cavities should prove valuable. One approach would be to develop better methods to assess the olfactory neuroepithelium and tongue as a means of looking for possible pathologic correlates of particular olfactory and gustatory disorders. Techniques worthy of special pursuit include evoked potentials, electrogustometry and advanced imaging technologies.

Affective Dimensions of Smell and Taste

There are important affective components to smell, taste and trigeminal stimuli. A major goal is to understand the normal and abnormal development of affective aspects in the chemical senses. Innate and experiential factors are believed to interact throughout the lifespan. There is also a need to understand changes in chemosensory sensitivity across the lifespan. A basic understanding of the factors associated with changes in chemosensory sensitivity and hedonics (pleasure) may indicate how better to alleviate the suffering associated with undesirable changes in sensory function. In addition, it will help in the treatment of conditions such as eating disorders that involve disturbances of chemosensory pleasure.

Chemosensation and Reproductive Physiology and Behavior

In addition to the olfactory receptor cells in the roof of the nasal cavity there are similar sensory cells in the vomeronasal organ located in the lower part of the nose. For many species of mammals, chemosensory stimuli, acting usually through the vomeronasal organ, are of primary importance in regulating reproductive physiology and behavior. Until recently it was believed that old world primates including humans did not possess a functional vomeronasal organ. Now, there is some contrary evidence. It is important to determine whether a functional vomeronasal organ exists in old world primates, including humans, using state-of-the-art anatomic, physiologic and molecular biological techniques. Potential clinical implications involve treatment for various abnormalities of reproductive physiology.

Impact of Smell, Taste and Touch Disorders on Nutrition, Chronic Illness, Safety and the Quality of Life

Loss or distortion of chemosensory function can impair food choice and therefore can increase the risk for poor nutrition. Salt-induced hypertension may be related to alterations of salt taste sensitivity. People with reduced olfactory or gustatory sensitivity may be unable to perceive bacteria or toxins in food and environmental stimuli, such as smoke and natural gas additives, that may warn of danger. Furthermore individuals with chemosensory complaints commonly report depression and impairment in the quality of interpersonal relationships.

Some chronic illnesses are associated with chemosensory symptoms that affect food intake. For example, taste loss or a persistent metallic taste can diminish food intake in persons with kidney disease. Other chronic illnesses associated with chemosensory dysfunction include diabetes, thyroid gland diseases and cancer. There are anecdotal reports of chemosensory changes associated with therapeutic drug use, but few controlled studies have evaluated these reports. Also warranting further study are the effects of local factors such as decreased salivary flow in Sjögren syndrome or radiation treatment of the oral cavity and pharynx.

Modeling at several different levels (such as behavioral, neurophysiological, and quantitative) is needed to characterize touch in individuals with normal sensation and those suffering sensory loss. By means of such models, it may be possible to characterize or predict the degree of loss of sensory and motor function and to assess their impact.

Effects of Occupational, Environmental and Infectious Agents on Smell, Taste and Touch Functions

Infectious agents, including rhinovirus, coronavirus, influenza virus and bacteria associated with sinusitis such as *Streptococcus pneumoniae, Hemophilus influenzae* and *Staphylococcus aureus,* may affect chemosensory function. Pollutants can cause serious damage to chemosensory systems necessary to warn and protect the individual against the hazardous environmental stimuli. Accordingly, there is a need to assess human exposure in polluted areas and in the workplace.

Inflammatory Mechanisms

Natural and acquired immunity defends the body against foreign substances such as allergens, infectious viruses, bacteria and fungi and toxicants. The body's response to a foreign substance can not only eliminate the substance but also alter existing structures. For example, white blood cells entering the nasal mucous membrane following an allergic response can damage the epithelium. These changes can resolve or lead to fibrosis. Consequently, there is a need to know whether inflammation prevents odors from reaching the olfactory neuroepithelium or actually damages the olfactory neuroepithelium. Additionally, it is important to know to what extent inflammation contributes to sensory loss after viral infection.

Touch

There are several environmental or occupational agents that may impair touch. Hand and arm vibration syndrome, also known as "white finger" syndrome, may result from prolonged exposure to vibration and may result in loss of sensitivity. An early sign of exposure to certain hazardous chemicals may also be the loss of sensitivity to touch. It is important to have measures of both normal and at-risk populations to determine the factors that affect and predict these disorders.

Strategies for Prevention, Management, Treatment and Rehabilitation of Smell, Taste and Touch Disorders

Treatment strategies for some chemosensory disorders are beginning to emerge. For example, topically applied corticosteroids have shown promise in restoring and improving olfactory function in some individuals. Clinical trials of such therapies are needed to assess their efficacy. Strategies for long-term management of chemosensory disorders need to be developed and communicated to health care professionals. Increased awareness of potential risk factors (detection of gas leaks and smoke), food selection and nutritional needs and compensatory adjustments to improve the quality of life are important issues for individuals with chemosensory disorders.

An extremely important function of the sense of touch in conjunction with kinesthesis is in aiding exploration, identification and manipulation of objects. These activities are part of tactile exploration of the environment. Systematic studies of tactile exploration of objects in persons without sensory losses are important in providing the means to evaluate individuals with neural and muscular deficits, as well as in charting the recovery from reconstructive surgery of the hand.

Providing adequate feedback and control for prosthetic hands and limbs depends upon an understanding of tactile perception. The need for information about tactile and tactile pattern perception is particularly great at the present time. The field of robotics and teleoperators requires such information to produce robotic sensors and manipulators and to provide feedback information to operators of these devices.

Research Opportunities

Basic Science Opportunities

Receptor cells for olfaction and gustation are at the interface of the external chemical environment and the organism. Mechanisms participating in the transduction of chemical stimuli into neural impulses include stimulus transport through mucus, binding to receptor proteins, interaction of multiple transduction processes and activation of specific mechanisms for stimulus metabolism and elimination. Within the central nervous system, various biologic processes of smell and taste are manifest in complex networks that include local circuits and close associations with multiple areas in the brain. Investigations that use single-cell isolation and recording techniques, biochemical, biophysical and optical methods, in vitro slice preparations, computational analyses, specific genetic strains of experimental animals, molecular and genetic probes and immunocytochemistry are essential for discovering the basic biology of information processing from receptors to the central nervous system. This basic information forms an essential underpinning for understanding chemosensory disorders.

Stimulus Characterization and Detection, Signal Transmission and Perireceptor Events

Molecular Bases of Olfactory Reception

The recent demonstration that a large, novel subset of genes encoding for proteins having seven-transmembrane domains is highly enriched in olfactory neurons, coupled with the cloning of molecular components of the transduction pathway, offer the opportunity to characterize in detail the mechanisms by which information about olfactory stimuli are transduced. These findings provide the opportunity for studying the molecular pharmacology of olfactory stimulus detection.

Research opportunities include to:

- Characterize the specific odorant recognition profiles of individual receptor molecules.
- Determine the coupling mechanisms between different receptors and second-messenger systems.
- Apply biophysical and optical recording techniques to determine stimulus specificity profiles and epithelial distributions of olfactory receptor neurons.

In other systems, tissue-specific gene expression is determined in part by the existence of genomic motifs that convey tissue specificity. In many cases, these motifs have been characterized both in vitro and in vivo and the proteins that regulate these events have been identified. Similar studies in the olfactory system have made possible the creation of transgenic animals in which exogenous genes are selectively expressed in mature olfactory neurons.

Olfactory receptor cells show different profiles with regard to stimulus specificity. What determines this specificity? Is it determined by the target or by the location of the receptor in the olfactory neuroepithelium? Does the phenotype of a cell change with stimulus exposure, with replacement or with age? Developments in molecular biology and with in vitro preparations make it possible to address these and other important issues.

Research opportunities include those to:

- Characterize the molecular mechanisms that determine olfactory-specific gene expression.
- Determine if genes that are selectively expressed in olfactory neurons have the same regulatory elements.
- Explore olfactory gene function by selective deletion of genes associated with reception, transduction, trophic interactions and neurotransmission.
- Identify the roles of newly discovered transcription proteins in determining olfactory-specific gene expression.
- Evaluate the metabolism of xenobiotic molecules and the distribution and role of odorant binding proteins.
- Identify the neurotransmitter(s) used at the first synapse of olfactory receptor neurons.
- Use new reverse transcriptase and polymerase chain reaction techniques to identify gene expression at the single-cell level.

- Use transgenic models for the study of receptor expression; sensory cell replacement; events determining cell death and replacement and connection with central targets.

- Generate functional cell lines to study cellular mechanisms of transduction and plasticity.

- Investigate possible genetic bases of chemosensory deficits in human and animal models.

- Learn how receptor specificity is determined by assessing the roles of sensory stimulation in gene regulation, connection with target and location in the receptor neuroepithelium.

- Evaluate the roles of anterograde and retrograde transneuronal influences on the development and phenotype of olfactory sensory cells and their target neurons.

- Determine the physicochemical and molecular correlates of odorant and nasal irritant potency and develop models to predict efficacy.

Taste Perception and Transduction

Reception and transduction in taste buds involves multiple mechanisms that include both taste-specific receptor proteins and apically located ion channels. The receptor proteins may interact with the taste-specific G-protein, gustducin or other G-protein subtypes to generate an electrical signal in the taste cell. The receptor proteins themselves have not been identified, and the exact role of gustducin in transduction is unclear. Molecular biologic approaches such as polymerase chain reaction should be used to identify and characterize possible taste receptor genes and confirm their specific expression in taste cells. Electrophysiological and optical recording techniques should be applied to acutely isolated receptor cells, as well as to receptor cells maintained in culture. Molecular biologic techniques should be applied to animal models with specific taste deficits to identify components in the transduction cascade.

Gustatory stimuli approach the taste receptors dissolved in saliva. Salivary composition is an important variable in taste transduction and perception. Knowledge of taste-salivary interactions is important for understanding the mechanisms of taste reception and transduction and taste disorders associated with altered salivary secretion.

Research opportunities include those to:

- Locate, isolate and characterize macromolecules used in taste detection and transduction.

- Apply electrophysiological and optical recording techniques to the study of taste transduction.

- Use existing animal strains and produce new animal models with specific taste deficits to identify and clone macromolecules involved in taste cell processing.

- Characterize salivary composition and its possible alteration by taste stimuli and hormonal factors.

- Identify potential tastant-binding proteins critical to the delivery of taste stimuli to the receptor cells.

- Determine molecular correlates of taste and oral irritant potency; develop quantitative structure-activity models.

Taste Receptor Tuning

The gustatory system responds to a variety of chemical stimuli. Whether individual taste cells respond to a broad or narrow spectrum of taste stimuli requires further analysis. Also unknown is whether morphologically distinct taste cell subtypes have distinct physiologic and molecular characteristics. Correlated structure-function studies are required in order to resolve these issues and to establish the specific role of the receptor cells in coding taste information.

Research opportunities include to:

- Apply electrophysiological and optical recording techniques to characterize the response of single taste cells to a variety of taste stimuli.

- Combine morphological, physiological, biochemical and molecular techniques on single taste cells to determine whether specific taste cell types respond selectively to specific taste stimuli.

Cellular Interactions within Taste Buds

Taste buds include a variety of components, such as receptor cells, basal cells and nerve fibers. The functional significance of the close packing of these varied elements into specialized end-organs is unclear. Studies in nonmammalian vertebrates have shown that electrical junctions couple the activity between adjacent cells, and chemical synapses have been found between receptor cells and basal cells. Whether these findings are applicable to humans is unknown. Trophic interactions between the nerve fibers and the cells within a taste bud are well known, but the mechanism underlying these interactions has not been fully described. Taste buds manifest poorly understood inhibiting interactions that can suppress taste responses for several minutes. Synapses from nerve fibers onto the taste cells are reported, but their function is unclear.

Research opportunities include to:

- Identify neurotransmitters and neuromodulators and their receptors in taste buds.

- Characterize the integrative properties of taste buds in signal processing.
- Investigate the trophic influences in taste bud development and maintenance using cell, tissue and tissue-slice culture techniques.

Hormonal and Systemic Influences on Taste Functions: Taste and Addiction

The sodium channel responsible for salt taste, the amiloride-sensitive sodium channel, also occurs in many salt-transporting epithelia. Several hormones, including vasopressin, aldosterone and atrial natriuretic factor, are known to regulate the expression of this channel in other transporting epithelia. Hormones may also regulate the expression of this sodium channel or other chemosensory transduction molecules in taste tissues. Experiments should be undertaken to test the effects of hormones on isolated taste cells or taste cells in culture. Molecular or biochemical probes should be used to test for the presence of hormone receptors in taste buds.

Various systemic diseases and drug therapy alter taste perception. The biologic modes of action of blood-borne chemicals on the sense of taste are poorly understood. New hypotheses are needed to explain such systemic influences on taste function.

Research has demonstrated that sugars and fats present in mother's milk profoundly decrease reactions to painful or stressful stimulation in rats and human infants. These antinociceptive actions of specific gustatory stimuli are blocked by opiate antagonists. These findings indicate that there are important, developmentally mutable linkages between chemosensory and pain control (brain opiate) mechanisms. Since these linkages may play roles in addiction, stress reactions and pain management, they merit further research.

Research opportunities include to:

- Use specific chemical probes to test for the presence of hormone receptors in taste buds.
- Characterize nutritional, hormonal and systemic influences on sensory responses of taste buds.
- Formulate and test hypotheses regarding the mechanisms underlying systemic influences on taste function.
- Determine the role of early taste experience in the development of brain opiate systems and their role in addiction and pain management.

Psychophysical and Neurophysiological Studies of Smell, Taste and Touch

Progress in understanding the processing of tactile stimuli will depend upon the continued close cooperation between psychophysical and neurophysiological studies. Progress has already benefited greatly from technical advances in the development of tactile stimulators.

Further research is needed to:

- Investigate psychophysical and neurophysiological correlates of spatial-temporal touch information.
- Develop and evaluate tactile displays.
- Encourage coordinate psychophysical and neurophysiological studies of smell and taste function.

Central Mechanisms: Neural Networks and Functional Integration

Olfactory Projections

Recent experiments with fish, amphibians and rats have demonstrated that olfactory receptor cells may not make point-to-point projections to the brain like the well-known topographic projections in touch where spatial localization of targets is paramount. Nonetheless, lectins and antibodies that are selective for subsets of olfactory receptor cells reveal that primary olfactory projections are highly organized. The emerging consensus is that olfaction (and perhaps gustation) lacks point-to-point projections and research should focus on functional projections.

Research is needed to:

- Carry out functional analyses of olfactory projection patterns by monitoring excitation and inhibition with such techniques as electrophysiological recording, voltage sensitive dyes, in situ hybridization or cytochemistry with antibodies, lectins or other probes for transcription factors, putative receptor proteins or their RNA message.

Olfaction: Neurotransmitters and Neuromodulators

Much has been learned of the patterns of neural connections in the olfactory system through the use of neuroanatomic techniques. However, the specific roles of these connections in the perception, identification and learning of specific olfactory cues and mechanisms mediating conscious sensation are not fully understood. For example, the neurobiologic basis of many behavioral capabilities, such as the ability to improve in the perception of particular sensory cues with experience and to discriminate constituents in odor mixtures, needs further study. Although there is evidence that levels of neural activity within olfactory structures can influence the synthesis of neurotransmitter and neurotrophic substances and the strength of synaptic connections, it is not known how these changes influence the processing of olfactory information. Progress on these issues will require better understanding of synaptic mechanisms at the molecular and membrane levels at the different neuronal levels in chemosensory pathways and characterization of the integrative properties of chemosensory neural networks and their linkages with other brain areas.

The last decade has witnessed an explosion of knowledge of integrative neural network function, transmitter action and cellular membrane properties of brain structure through the use of in vitro tissue slice and organotypic culture preparations as well as computational modeling approaches. These important tools have had only limited use in studies of the olfactory system. The development and use of olfactory bulb slice preparations, particularly in mammals, should be accorded a high research priority.

Further work on the impact of particular disease states on chemosensory processing might also illuminate functional contributions of particular brain regions and neuronal groups.

Research opportunities include those to:

- Identify the neurotransmitters, neuropeptides, receptors and second-messenger systems throughout the olfactory system.
- Identify the roles of olfactory axons in the developmental induction and maintained expression of neurotransmitters in postsynaptic, olfactory-bulb neurons.
- Evaluate the status of olfactory-bulb, dopamine neurons and their role in sensory disorders associated with Parkinson's disease.
- Determine the mechanisms underlying postsynaptic responses of neurons in central olfactory networks.
- Characterize the roles of neural activity and transmitter actions on gene expression in olfactory neural networks.
- Determine the neural circuits activated during different stages in the processing of olfactory, gustatory and tactile information to identify the influence of arousal and motivation on sensory perception, discrimination and learning.
- Develop mammalian olfactory-bulb, in vitro, slice and organotypic slice preparations to study membrane, biophysical properties, transmitter function and neural network, integrative functions.
- Employ electrophysiologic, recording techniques in anesthetized and free-moving animal models to characterize neural-network function at all levels of the olfactory system.
- Develop "biologically realistic," neural-network-based, computational models for regions

subserving the olfactory, gustatory and tactile sensations to identify mechanisms of sensory processing and learning.

Odor Perception and Cognitive Processes

Opportunities exist for better understanding of odor quality perception, particularly of complex mixtures. Experiential (such as adaptation and habituation), developmental, contextual and aging factors that affect the accuracy of recognition of odor components need to be identified. The mechanisms by which perceptual constancy is achieved under varying physical conditions should be better understood. Understanding higher olfactory function thus necessitates perceptual studies of odor recognition and factors that affect the accuracy of those processes. Moreover, the contributions of the several brain areas involved in aspects of quality perception, odor identification and learning should be studied.

Research is needed to:

- Evaluate the dynamics of olfactory adaptation, cross-adaptation and habituation.
- Investigate factors affecting odor recognition of complex mixtures.
- Identify the components of odor processing (recognition, identification, categorization, learning and recall) of different olfactory brain areas.
- Characterize the patterns of impairment in the processing and learning of sensory information in humans with neurodegenerative disorders that damage neurons in the chemosensory and tactile systems to elucidate the roles of those structures in sensory function and cognition.

Feedforward and Feedback Regulation of Olfactory Function

A unique feature of the olfactory system is the high degree of feedforward and feedback that characterizes olfactory neural networks. Olfactory-bulb, output neurons receive massive feedback from all their target structures. This arrangement implies that central neurons actively modify signal processing at the earliest levels of synaptic integration in the olfactory pathway. The functional significance of this unparalleled degree of network reciprocity is unknown, but it strongly implies parallel rather than serial processing mechanisms. Neurophysiologic studies are needed to elucidate the significance of this unusual aspect of olfactory network organization.

Studies are needed to:

- Determine the functional importance of central feedback to the olfactory bulb in odor detection, recognition and learning.

Taste: Neurotransmitters and Neuromodulators

Although progress has been made in describing neurotransmitters in central gustatory nuclei, the transmitters used by the primary gustatory nerves and brain stem gustatory neurons are unknown. Probes now available to identify many neurotransmitters and their receptors should be used to determine the principal neurotransmitter and neuromodulator systems in gustatory networks. Excitatory, inhibitory and modulatory actions of identified neurotransmitters on neurons in central gustatory centers should be investigated.

Research opportunities include those to:

- Use biochemical and molecular probes to identify the neurotransmitters and receptors involved in the central processing of taste information.
- Determine the mechanisms underlying postsynaptic responses of neurons in central gustatory nuclei to neurotransmitters.

Central Representation of Taste Quality

Taste quality may be encoded centrally through the mechanism of chemotopic maps analogous to the tonotopic map found in the auditory system. Alternatively, chemical quality may be encoded by patterns of activity in discrete neuronal ensembles as color is encoded in the visual system. More complete information on the response properties of neurons in central gustatory centers is necessary to test these alternatives. Neural-network models of gustatory processing should be developed.

Research opportunities include those to:

- Use physiological and optical recording methods including voltage sensitive dyes to determine how taste quality is represented in the central nervous system.
- Develop computational and conceptual models of gustatory processing.

Neural Circuits Underlying Taste-Mediated Behavior

Taste is important for various ingestive, digestive and protective responses, including chewing, swallowing, salivation, gastric changes and gagging. The solitary nucleus contains local circuits connecting the gustatory input to motor centers serving these behaviors. In addition, gustatory inputs are relayed to higher regulatory areas that regulate feeding and drinking. Conditioned flavor aversion is an example of a particularly potent and persistent one-trial learning. The circuitry and complex, neural interactions underlying such aversions warrant further investigation. The role of the gustatory thalamus, basal forebrain and neocortex in taste function is largely unknown, in sharp contrast with the wealth of information available about forebrain processing in other sensory systems. Knowledge of forebrain networks, the location of neurotransmitters and neural function is badly needed. Much has been learned about taste cell-taste nerve plasticity in normal turnover and following injury and regeneration, but nothing is known about the reorganization of the neural circuits in gustatory brain networks in these same conditions. There is a need to determine if changes in peripheral cell-cell interactions are accompanied by central reorganization.

Research opportunities include those to:

- Characterize neural circuits and neurotransmitters subserving taste-mediated ingestive, digestive and protective responses.
- Analyze the neural circuitry and neurotransmitter systems underlying conditioned flavor aversions.
- Analyze forebrain neural networks involved in gustatory processing to identify circuit organization, neurotransmitters and the physiologic principles of taste coding.
- Characterize the reorganization in the gustatory portion of the central nervous system after damage to the taste system by depletion or trauma.

Cognitive Processes in Touch

As is true for other sensory modalities, the experience of touch is highly dependent upon cognitive processes such as attention, learning and memory. Studies of touch perception affected by these processes may prove particularly important as research progresses from investigations in the laboratory to clinical studies.

Research is needed to:

- Examine the role of cognitive processes in the perception of cutaneous and oral, tactile stimuli.

Active Perception in Smell, Taste and Touch

Research opportunities exist to understand the nature of odor perception when expectancies are manipulated and specific target odors are sought. The interplay of learning and experience on odor perceptions should be investigated.

Active perception is an inherent aspect of astringency perception in that astringency would seem to require mouth movements for accurate evaluation. Mouth movements, especially chewing strategies and chewing effectiveness, should be studied for their effects on taste, oral touch and retronasal smell perception.

Investigation of astringency should be focused on more complete qualitative and quantitative psychophysical characterization, understanding the relationship between chemical structure and astringent impact and interactions of astringent stimulation with salivary constituents with tastants and with other trigeminal chemical stimuli. Since astringents induce a kind of artificial xerostomia (dryness of the mouth), studies should be conducted to explore the parallels and differences between astringency and various syndromes of dry mouth (such as Sjögren syndrome).

Research opportunities include those to:

- Investigate active perception and purposeful sensation seeking in the chemical and tactile senses and contrast sensory effects from actively sought stimulation with passively imposed stimulation.
- Characterize the sensory elements associated with oral texture, temperature and viscosity.
- Investigate the chemically induced modulation of oral tactile sensations, including touch (e.g., astringency), temperature and pain.
- Explore how the properties and perception of mixtures of odorants, tastants, astringents and irritants relate to the properties and perception of unmixed stimuli.

Touch and Its Interaction With Other Senses

The experience of touch depends upon inputs from various modalities. Touch contributes to eating behavior and the experience of food more generally. Touch also is an important component in balance and is critical in the perception and manipulation of objects.

Research is needed to:

- Study interactions among the cutaneous senses, including touch, temperature, pain and itch at both the psychophysical and neurophysiological levels.
- Determine the anatomical, behavioral and physiological bases for interactions between the cutaneous senses and smell and taste.
- Develop models for shape perception, object identification and event perception that incorporate touch and kinesthetic information.

Plasticity, Including Development, Regeneration and Aging

Causal Role of the Olfactory Placode in Central Nervous System Development

There is evidence that the development of the olfactory organ influences the development of the brain. When precursors of the frog olfactory placode are removed, development of the brain is severely impaired. Reduction of the number of olfactory axons results in corresponding reductions in the number of output neurons (mitral cells) in the frog olfactory bulb. Olfactory receptor cell axons appear to play a key role in olfactory bulb development and are in direct contact with neuronal precursor cells. Pioneering olfactory axons alter the cell cycle of olfactory bulb precursor cells and cause the daughter cells to exit the mitotic cycle and differentiate into olfactory bulb neurons and glia. This mechanism may involve trophic and mitogenic signals.

Some conditions of abnormal brain development in humans may be traceable to biochemical deficits of nasal origin. This hypothesis is strengthened by the observation that humans born with certain central nervous system anomalies (such as Kallmann syndrome) also have olfactory deficits.

In clinical terms, anencephaly may be produced by a primary dysfunction in the development of the olfactory system. It would be valuable to conduct teratologic studies in humans and animals of the nose-brain relationship from clinical, experimental and genetic points of view. Key to the identification of factors and genes responsible for these processes is the development and use of organotypic tissue culture models. These preparations allow molecular dissection and perturbational studies of developmental processes that take place in vivo and are difficult to manipulate.

The olfactory receptor neuron is the only known nerve cell in mammals, including humans, that can be replaced or grown back throughout the full lifespan of the organism. This extraordinary neuron can reestablish functional synaptic connections with its target cells in the brain. It can also establish synaptic contacts with nonolfactory neurons. Thus, olfactory neurons provide an important and unique cell that may be able to repair the damaged nervous system following stroke, neurodegenerative diseases and injury, including spinal cord injury. In other parts of the brain, injury causes glial cells to react and form barriers to normal repair. Research suggests that olfactory glia are different and may actually promote the growth of new axons. The unique properties of olfactory glia should be studied further. New techniques of cellular and molecular biology and gene transfer may be adapted to induce olfactory neurons to replicate in nonolfactory parts of the brain or to produce molecular and cellular environments to restore function of the damaged brain.

Investigators are learning how to grow olfactory neurons in vitro. In the future, neurosurgeons may be able to use such neurons in transplant procedures, replacing damaged tissue. Just as kidneys and hearts are now being transplanted, it may be possible to transplant olfactory neurons into the damaged central nervous system.

Research opportunities should include those to:

- **Identify the cellular and molecular factors that allow olfactory neurons to grow to and enter the central nervous system.**
- **Identify the factors by which incoming olfactory axons influence the mitotic cycle and differentiation pathways of olfactory-bulb precursor cells.**
- **Characterize the cellular and molecular mechanisms by which olfactory neurons induce and maintain the olfactory bulb.**
- **Characterize cellular and molecular features that distinguish olfactory glia from other glial cells.**
- **Develop organotypic and cell culture models to allow manipulative studies of early events in olfactory-system development.**
- **Develop genetically modified cell lines and transgenic animals to allow identification of factors and genes important for olfactory-system development.**

Signals Controlling Olfactory-System Development

It is clear from recent work that there are reciprocal interactions between peripheral olfactory neurons and their central nervous system targets. Trophic factors, adhesion molecules, mitotic regulators and other molecular signals are important for initiating and maintaining development of the olfactory bulb. These molecular signals may influence development by interacting with glia, precursor cells and neurons. In addition, similar factors or molecules maintain mature olfactory receptor cells in adults. It has been demonstrated that the expression of neurotrophic factors by neurons and glia can be modulated by levels of neuronal activity, injury, cell death, circulating hormones and synaptically released transmitters.

Research opportunities should include studies to:

- **Identify the cellular, molecular and genetic factors that regulate olfactory receptor cell neurogenesis, maturation, senescence and death.**
- **Identify transient and permanent cell contacts and molecular interactions among olfactory receptor cell axons and precursor cells, glial cells and neurons in the developing and adult olfactory bulb.**
- **Characterize trophic interactions among olfactory receptor neurons, the olfactory bulb and neurons comprising central olfactory pathways.**

- Identify and characterize guidance-recognition mechanisms for migration, axon growth and synaptogenesis in the olfactory system.
- Locate, identify, and characterize segmentation and homeotic genes in olfactory development.
- Determine the role of immediate early genes and other transcriptional regulatory genes in olfactory-system development and plasticity.
- Determine the influence of hormones, neurotransmitters and peptides in olfactory-system development.

Primary Cell, Organotypic Cultures and Immortalized Cell Lines for Use in Understanding Olfactory Mechanisms and Neural Transplantation

Primary and clonal cell cultures from the olfactory neuroepithelium have been very difficult to produce. A few laboratories, however, have determined culture conditions that permit mitotic activity in the basal cells as well as survival and differentiation of olfactory receptor cells. More work is needed to determine the specific cellular and molecular mechanisms controlling mitotic activity, differentiation, maturation and survival of olfactory receptor cells.

Explants of olfactory neuroepithelium can be introduced into the central nervous system. Basal cells within these transplants continue to divide, and the olfactory neurons send out axonal processes into the brain tissue.

In mammals, including humans, most of the important events in olfactory development occur *in utero*. As such, these events are less accessible to surgical and molecular dissection, such as blocking key molecules or selectively killing specific cell types. Dramatic advances in the developmental neurobiology of other sensory systems is being achieved by the development and use of explanted, tissue-slice culture systems that survive and grow in a highly organotypic fashion. State-of-the-art cellular and molecular manipulation can be applied to such cultures to identify and manipulate developmental mechanisms. The development of organotypic, olfactory, culture models will allow exploitation of modern molecular and cellular approaches to study olfactory development.

Molecular genetic techniques can be used to insert genes into cell lines. In addition, genetic engineering of precursor cells can produce immortalized cell lines with new genes for cell labeling and potentially introducing new gene functions. In other systems, these cell lines have been transplanted into target tissues where they differentiated and formed synapses with host neurons. Development of genetically engineered, immortalized olfactory cell lines may prove useful in promoting the repair and replacement of damaged or diseased neurons and neural networks in the central nervous system.

Research opportunities include those to:

- Develop further and use olfactory-neuroepithelium-derived, primary cell cultures to determine the factors that regulate mitosis of basal cells and the differentiation, survival and functional expression of receptor and transduction molecules.
- Develop and use organotypic slice cultures of the olfactory bulb and placode to characterize and manipulate the cells, molecules and genes that determine olfactory-system development.
- Investigate the ability of cultured olfactory neurons, glia and genetically transformed olfactory neuronal cell lines to enhance the growth-promoting microenvironment and to repair damaged pathways and circuits in the diseased or injured brain.

Aging and Cell Death in Olfactory and Gustatory Epithelia

Olfactory neuroepithelium is a unique, natural model for neuronal aging and cell death. Olfactory receptor neurons are replaced throughout life, but the events leading to the death of these cells are unknown. There are a variety of hypotheses about different mechanisms leading to cell death, including unregulated calcium buffering, loss of trophic support or responsiveness and the expression of specific "death genes." Moreover, the expression of other genes has been associated with promoting cell survival in a variety of adverse conditions, including hypoglycemia, over-excitation, ischemia and exposure to xenobiotics. The roles of immune response elements in the death, remodeling and healing responses of the olfactory receptor neurons are poorly understood. The olfactory neuroepithelium should be used to test mechanistic hypotheses of neuronal cell death and to search for protective and stimulatory factors that extend the viability of these neurons.

Specifically, research opportunities include those to:

- Study the pattern of gene expression preceding the death of olfactory receptor cells to identify the presence of "death genes" and the expression of genes that prolong viability.
- Determine the role of heat-shock and other proteins in the processes of cell death.
- Determine the integrity of calcium buffering and the activity of calcium-activated, proteolytic enzymes within olfactory neurons over the lifespan of the cell.

- Determine the trophic agents that support the olfactory receptor neurons and the normal sources of trophic support.

- Determine the role of macrophages and other immune-response elements in damage, healing and cellular replacement in the olfactory neuroepithelium.

Taste Bud Development and Turnover

Recent work has outlined some of the major morphogenetic events in the formation of taste buds and taste papillae. This work should be followed by cellular and molecular studies that analyze cell lineages and cell-cell interactions, including axon-epithelial cell interactions, in the gustatory epithelium.

Cell surface and extracellular matrix molecules may play important roles. In particular, it is important to develop cell markers that identify taste cells with respect to lineage, age, differentiation and function. Molecules associated with transduction which have been identified (e.g., gustducin and amiloride-channel proteins) may be useful as markers. With new markers for taste cell-associated molecules, it would be appropriate to use nerve crossing techniques to determine whether the presence of such molecules is tissue or nerve specific. Protein kinase receptors and transcription factors may reveal information about a taste cell's developmental state or neurotrophic dependence.

Although it has been established that axonal transport is necessary for the structure and function of mammalian taste buds, there is little information on the putative molecules or cell-cell interactions that mediate support. With improvements in cell and tissue culture methods and the increasing number of identified trophic agents, it seems propitious to attempt to culture taste cells. A culture system for taste cells would facilitate exploration of many of the opportunities described above.

Research opportunities include to:

- Identify the origin, diversity and lineage of taste receptor cells.

- Characterize the trophic influences in taste bud development and maintenance.

- Define the synaptic connectivity between taste buds.

- Study cell death and replacement of taste receptor cells.

Development of Electrophysiologic Responses to Taste Stimuli

The role of taste in suckling should be more closely evaluated. The taste of milk might promote suckling in newborn mammals with functioning taste buds. Lactose is the main sugar in milk. However, lactose has rarely been one of the sugars used in the behavioral or physiological analyses of developing taste responses.

Non-precocial animals, like rats, are particularly convenient for analyzing developmental changes because their taste buds do not mature until after birth. Changes in IXth cranial nerve responses could be examined during the first and second postnatal month in tandem with the increasing numbers of foliate and circumvallate taste buds.

Studies have shown that the rate of development of salt taste is species-specific and even nerve-specific. Are species that have slow, salt-taste development those that prefer salt behaviorally? Does a taste for salt compete with suckling? The early development of a salt preference could lead the neonate to lick at urinary salt, thereby interfering with suckling.

The tendency of peripheral taste nerve responses to develop before central responses suggests that functional input may modulate brain circuits.

Research opportunities include to:

- Examine the development of responses to lactose.
- Examine the development of taste responses, especially bitter responses, from the posterior one-third of the tongue during the postnatal period when taste buds in this region mature and accumulate.
- Determine whether species that have a behavioral preference for salt also have delayed physiologic development of salt taste.
- Assess the role of peripheral control of central taste circuits in development and during normal, taste-cell turnover and replacement.

Markers for Taste Cells In Situ and in Tissue Culture

Differentiated taste receptor cells may have specialized molecular structures that could serve as specific markers. If recent success in finding taste cell markers can be expanded and exploited (e.g., cell adhesion molecules and keratins), it should facilitate analyses of the development, degeneration, regeneration and culture of taste buds. Recent improvements in culturing techniques increase the likelihood that taste buds can be cultured.

Research opportunities include to:

- Develop markers for differentiated taste cells, including different types of taste cells.
- Use markers and improved culture techniques to determine the factors that regulate differentiation of taste cells.

Chemosensory Systems and Aging

Although declines in chemosensory acuity are associated with aging, the biologic bases of these changes are not understood. Olfactory neurons are lost during aging in some species, whereas rather constant numbers of taste buds apparently are maintained in humans, nonhuman primates and rodents. Neural taste responses indicate robust gustatory function in old rodents. Although olfactory receptor cells decline in number, new neurons continue to be produced in old rodents. There is no information, however, about chemosensory receptor changes at the biochemical, membrane or cellular levels, and there is almost no information about age-associated differences in central olfactory and gustatory systems. Fundamental neurobiologic studies are essential as a basis for understanding smell and taste disorders in the elderly.

Research is needed to:

- Explore the phenomenon of senescence in olfactory and gustatory systems to understand age-related chemosensory disorders.

Role of Experience and Touch

Recent studies with adult monkeys have revealed considerable cortical plasticity as a function of experience. Paralleling these charges in central organization are changes in behavior in animals and evidence that human subjects show altered sensory experience as well. These results have important implications for understanding basic cortical and subcortical brain mechanisms, as well as for the recovery of function following injury.

Research is needed to:

- Investigate the role of experience in altering tactile sensitivity and reorganization of the central nervous system.

Clinical Science Opportunities

Epidemiology of Smell, Taste and Touch Disorders

Accurate information is needed on the incidence, prevalence and risk factors of anosmia, hyposmia, parosmia, ageusia, hypogeusia, dysgeusia and tactile disorders. There is also a need to know the natural history, including age of onset and duration of these disorders. Obtaining the required information will entail a major national study that avoids selection and access problems and that addresses etiologic, geographic and occupational factors, aging and dementia, gender differences, cultural factors, environmental exposure, and genetic and socioeconomic factors. Prognosis by etiologic categories also should be addressed.

Etiology of Smell, Taste and Touch Losses

Major causes of anosmia and hyposmia are upper respiratory infections, head trauma, nasal and paranasal sinus disease (including allergic rhinitis and nasal polyposis), some neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease and some genetic disorders such as Kallmann syndrome. Exposure to inhaled toxic chemicals, particularly in the workplace, also may result in a loss of the sense of smell. In addition, there is a well-documented decrement in the sensitivity of the senses of smell, taste and touch with aging. Furthermore, certain therapeutic regimens (e.g., radiotherapy and surgery of the head and neck region and use of pharmacologic agents such as antihypertensive drugs and antibiotics) can adversely influence chemosensory function.

Taste losses accompany smell losses in some individuals with the causes of olfactory losses noted above. In addition, taste loss occurs with neural damage associated with such conditions as Bell's palsy, Ramsay Hunt syndrome and some strokes.

Etiology of Parosmia and Dysgeusia

In the chemical senses, individuals may perceive sensations for which there are no obvious stimuli. Dysgeusia is a chronic, usually unpleasant taste that often occurs in the absence of obvious stimulation. It is the chemosensory complaint most resistant to diagnosis and treatment. Dysgeusia can originate because a hidden stimulus in the mouth produces the taste or because of abnormal activity of the receptor cell or its central connections. Known causes arising in the peripheral nervous system include taste nerve compression or stretch. Known causes arising in the central nervous system include epilepsy and tumors.

Parosmia, like dysgeusia, may involve a chronic, usually unpleasant, odor perception that occurs in the absence of external stimuli. An abnormal perception may be substituted for the usual perception (e.g., spoiled meat for mint). These substitutions may be triggered by an odorant or may occur spontaneously. Dysgeusia and parosmia can be distinguished by descriptors used by the person experiencing the condition. Dysgeusia involves the use of the four taste-quality names (sweet, salty, sour and bitter or metallic). Parosmia descriptors may be the names of objects with particular odors (such as gasoline or garbage), or the individual may not be able to provide any description other than unpleasant. Parosmia may be associated with conditions of degeneration or regeneration of olfactory tissue. Like dysgeusia, it may simply reflect perception of a stimulus that is actually present, such as those resulting from purulent rhinorrhea or infectious processes in the nasal cavity or it may result from activity in the central nervous system. For example, some patients with temporal lobe epilepsy perceive an olfactory aura (warning). Severe parosmia can be such a debilitating disorder that some patients have sought surgical relief by removal of the olfactory bulbs.

Research opportunities include those to:

- Determine the incidence, prevalence and risk factors of anosmia, hyposmia, parosmia, ageusia, hypogeusia, dysgeusia and hand/arm vibration syndrome and other tactile disorders.
- Determine the course of these disorders over time.
- Determine how the genes determining Kallmann syndrome alters chemosensory function.
- Investigate the genetic bases for chemosensory disorders.
- Determine the bases for idiopathic congenital anosmia.

Chemosensation in Systemic Diseases

Altered chemosensory sensitivity may accompany certain systemic diseases, including hepatic failure, pseudohypoparathyroidism (hereditary disorder characterized by low blood calcium that is unresponsive to parathyroid hormone), diabetes and hypertension. Smell losses are observed during the course of Parkinson's disease, Alzheimer's disease and AIDS dementia complex. These losses may appear early in the disease processes and show progressive change as a function of the disease state. Losses in the sense of smell in Korsakoff's psychosis (chronic alchoholism-induced dementia) correlate with the diminution of the major metabolite of norepinephrine (a neurotransmitter) in the cerebrospinal fluid. Smell- and taste-conditioned aversions are common in patients with neoplastic diseases, particularly following periods of chemotherapy. The role of G-proteins should be studied, as should the mechanism of chemosensory loss in pseudohypoparathyroidism. Chemosensory losses may provide a simple and noninvasive early means of detecting neurodegenerative diseases such as Alzheimer's disease, thereby leading to new insights into etiology and early intervention.

Research opportunities include those to:

- Find the cause for disorders of chemosensory sensitivity in systemic diseases.
- Identify the drugs that alter chemosensory perception either positively or negatively and determine their mechanism of action.
- Explore the extent and type of olfactory impairment in individuals with AIDS dementia complex and determine the degree of central and peripheral involvement.

- Determine the pattern and extent of olfactory loss in Alzheimer's disease and related dementias, their association with underlying neuropathology and the prognosis for recovery.
- Investigate the functional lateralization of olfactory processing.
- Investigate the consequences of high maternal salt intake on offspring's salt intake, salt-taste sensitivity and salt preference and the relation to blood pressure in humans.
- Determine how inflammation occurring in the olfactory cleft affects olfactory tissue.
- Determine whether inflammation can lead to irreversible impairment of smell, taste and touch.
- Investigate longitudinally the contributions of lifelong nasal allergy, inflammation, chronic sinusitis and exposure to environmental agents on olfactory sensitivity in the elderly.

Development of Diagnostic Tests

Psychophysical procedures are currently being used to evaluate smell and taste. They involve threshold detection, quality identification, confusion among stimuli and suprathreshold scaling of perceived intensities. Taste testing uses the whole mouth or can be restricted to regions of the mouth. Olfactory testing can be limited to one nasal cavity. In both olfaction and gustation, current psychophysical tests do not help establish the cause of the disorder.

Improved olfactory tests are needed to indicate, for instance, whether the lesion is traceable to the central nervous system, whether it is based upon a deficit in the olfactory nerve or trigeminal nerve, or whether it is attributable to airflow occlusion. Such testing may require a more careful selection of odorants. The odors misidentified might reflect the underlying causal mechanisms. The actual nature and number of odorants which are misidentified by a patient performing the test may be diagnostic for a particular chemosensory disorder. New test strategies to identify the causes for smell and taste disorders are needed.

Are there specific anosmias, olfactory losses specific to particular odorants? The results would not only provide clues to the cause but also would have implications for a conceptualization of the process underlying olfactory discrimination.

In the sense of taste, losses are already known to be specific to taste qualities. But can the loss be differentiated within a single quality? For example, can the ability to taste some sweeteners be reduced while others are spared in disorders or aging?

Research opportunities include those to:

- Develop diagnostic methods for specific smell and taste disorders.
- Improve the objectivity of psychophysical measures, eliminating the need for verbal responses by the subject.
- Develop new instrumentation for monitoring the time course of chemosensory disorders.
- Evaluate evoked potentials and electrogustometry for clinical diagnosis.
- Devise chemosensory-based diagnostic strategies to differentiate among types (cortical or subcortical) of dementias, for example, Alzheimer's or AIDS-related, which have associated olfactory impairments.
- Develop molecular probes that may be of prognostic value in evaluating persons with chemosensory disorders.
- Explore the use of advanced brain imaging techniques (such as computed tomography and magnetic resonance imaging) in the diagnosis of smell, taste and touch disorders.
- Identify markers in, or physical parameters of, body fluids or secretions that provide corroborative diagnostic indicators of chemosensory dysfunction.

Genetic Variation

Because of genetic variation, people differ in their ability to explore chemosensory worlds. As noted in the National Geographic Society survey, not all individuals can smell certain odorants. Similarly, all individuals are not equally able to taste certain bitter and sweet compounds. However, relatively few of the many olfactory and gustatory molecular stimuli that may show the effects of genetic variation have been explored.

Genetic variability may underlie some of the variation in preferences for foods and beverages. The potential economic impact is illustrated by consumer acceptance of artificial sweeteners. Aspartame quickly became the artificial sweetener of choice when compared to saccharin. That occurred in part because saccharin has a bitter taste to many people.

Research is needed to:

- Study the impact of genetic variation on perceptions of odorants and tastants.

Olfactory Pathology

The diagnosis and treatment of olfactory disorders have been made difficult by a lack of knowledge of the pathology, especially the neuroepithelial pathology, of olfactory dysfunction.

Since the technology for performing safe biopsies of the olfactory neuroepithelium of humans has become available, it has become possible to search for characteristic morphologic, biochemical and biophysical features of the elements of the neuroepithelium of individuals having the same olfactory disorder. If consistent features exist, individuals may be able to benefit from better diagnostic evaluation through the use of neuroepithelial biopsies. Similarity of findings in humans with olfactory disorders and animal models of disease would increase the likelihood of the clinical relevance of therapeutic maneuvers in animal models.

Research opportunities include to:

- Evaluate the potential use of biophysical, biochemical, molecular biological and immunobiochemical studies of biopsy material to diagnose olfactory disorders.
- Determine whether immortalized cell lines can be produced from olfactory neuroepithelial biopsies or fetal material and evaluate, in animal models for future potential human explants, whether genetically altered olfactory-cell lines might be useful for treating various central nervous system diseases.

Gustatory Pathology

Taste papillae can readily be tested for taste sensitivity before they are either removed from the tongue for analytic processing or studied by means of videomicroscopy of the tongue. The technology for this work is now available.

Research is needed to:

- Relate lingual and mucosal lesions to taste disorders.

The taste system has built-in redundancy, and some losses of taste sensitivity go unnoticed. To gather clinically relevant taste data, study populations potentially at risk for taste disorders are needed. They include groups of individuals with Bell's palsy (viral facial paralysis) and Ramsay Hunt syndrome (herpes zoster infection of facial and acoustic nerve ganglia resulting in facial paralysis, hearing loss and vestibular disturbances). There are numerous anecdotal accounts of the effects of drugs on taste, but they remain unsubstantiated by controlled studies.

Research opportunities include to:

- Identify, survey and study human populations at risk for loss of the sense of taste.
- Identify those drugs reported to alter the sense of taste and validate the effects under controlled studies.

Animal Models

One approach for identifying the mechanisms basic to particular olfactory or gustatory dysfunction is to produce the same dysfunction in animals. For instance, animals now can take the same odorant confusion matrix test as humans. By perturbing the animal's olfactory system to produce a similar pattern of odorant confusions as observed in humans, common mechanisms of olfactory dysfunction may be identified.

Research opportunities include those to:

- Develop animal models for the study of chemosensory deficits and excessive intake of nutrients such as sodium that is mediated by taste.
- Test the effects of drugs on behaviors mediated by smell and taste in animals.

Diagnosis of Touch and Related Disorders

It is increasingly apparent that some individuals with smell and taste disorders also have altered or impaired touch in the oral and nasal region. In cases of injury or in some diseases, there may be an associated loss of touch information. The loss of touch may be of value in the diagnosis, may be a problem itself or may be a marker in the rehabilitation process.

Research is needed to:

- Develop devices and techniques for testing the facial and oral sensitivity of individuals without taste disorders and those with taste disorders.

Lifespan Development of Sensory and Affective Response

Before birth, the human fetus can probably smell and taste. How sensitivity to odors and tastes changes during infancy and childhood remains largely unexplored, in part because measurement techniques are not well developed. The development of affective responses to smell, taste and trigeminal stimulants also remains a puzzle. Affective responses to some tastes, such as sweet and bitter, are evident even in premature infants, although they may change, perhaps with changes in sensitivity, during the lifespan. For salt, there appear to be clear developmental changes in postnatal sensitivity and preference. How environmental factors may impact taste sensitivity and preference need to be investigated, particularly since some chronic diseases may be exacerbated by excess consumption of taste stimuli such as salt.

It is unclear from the evidence whether the positive and negative affective responses elicited by certain odors are innate or acquired from early experience or learning. Odors play an important role in mother-infant interactions. Flavors (odors and perhaps tastes) consumed by the mother are experienced by the very young infant and infants have adultlike hedonic responses to some odors and tastes within a few hours of birth. Recent evidence suggests, however, that even adult experience may increase sensitivity to some odors to which individuals were previously insensitive, perhaps through a process of receptor amplification. In humans, chronic maintenance on a low-sodium diet reduces the preference for sodium chloride in foods. Research is needed to clarify the role of specific experience in the development of persistent food preferences and aversions that may have an impact on nutritional status across the lifespan.

Changes in affect and sensitivity can also occur in adulthood. Some individuals suffer the chronic presence of unpleasant odors and tastes in the absence of obvious stimulation. These sensory phantoms can make eating so unpleasant that a marked weight loss results. Research is needed to determine in detail how the diet is altered by these dysfunctions, giving special attention to the nutritional risks engendered.

The affective responses associated with smell and taste may be disturbed without concomitant changes in sensitivity. For example, patients with eating disorders (anorexia nervosa or bulimia) show abnormal affective responses toward food without changes in smell and taste sensitivity. In addition, long-term food preferences and aversions can be conditioned. Cancer chemotherapy provides a vivid clinical example of conditioned food aversions. People experiencing nausea from chemotherapy can develop aversions to foods consumed before the therapy. That is believed to account, in part, for the appetite loss that often accompanies chemotherapy. Aversions can be prevented to some degree by the administration of a novel flavor before chemotherapy. The aversion tends to be conditioned by the novel flavor and spares the diet. Conditioned food aversions have proven beneficial under some circumstances. Alcoholics have been helped to abstain from the beverages they abuse by forming conditioned aversions to those beverages.

Studies of animal models demonstrate that olfactory stimuli play a role in sexual behavior, reproduction and maternal behavior. Some studies suggest that these behaviors have unlearned components, mediated through a specialized chemosensing organ called the vomeronasal organ. It is possible that humans also possess a vomeronasal organ and that human behavior may be similarly regulated. Studies are needed to clarify the interaction between genetic and environmental influences, as well as the extent to which odors are involved in control of social and sexual behavior in reproductive physiology in humans.

Research opportunities include those to:

- Determine how dietary and environmental odorant and tastant exposure modulate sensitivity and affective responses to these stimuli and impact on nutrition.

- Evaluate chemosensory sensitivity in infants and young children by means of new techniques that are sufficiently sensitive to serve as an effective clinical procedure.

- Determine the role of chemosensory stimuli in human social and sexual behavior and reproductive function.
- Determine how changes in affective responses to chemical signals influence patients' prognoses.
- Examine how olfactory and gustatory sensitivity vary over time in the same individual.
- Examine individual differences in olfactory sensitivity and seek predictors and correlates of high and low sensitivity.

There is considerable interest in the development of touch both in its own right and as an indicator of normal development. There remains a difficulty in delivering quantifiable tactile stimuli and in interpreting the results of tactile measurements. There also is an obvious and close relationship between the experiences of smell and taste and touch, particularly in infants.

Research is needed to:

- Encourage the development of standardized measures of touch sensitivity suitable for infants and throughout development.

Aging

Aging takes a greater toll on olfaction than on gustation. Since olfaction provides the cues used to identify many foods (for instance, chocolate versus vanilla), losses in olfaction diminish the pleasure associated with eating.

There is controversy about whether the losses in olfactory ability are uniform across odorants. This question is not only of basic interest, but it has many practical implications. The odorants placed in natural gas to warn of leaks cannot be perceived by some elderly people at the levels now employed. Attention to the level of odorant and to types of odorants screened for perceptibility in the elderly is needed.

The fact that age has less impact on taste appears to result partially from redundancy in the taste system. The elderly do show greater losses for some taste qualities than for others. Nonetheless, taste losses put older persons at risk for serious consequences if additional olfactory losses occur. Some elderly people experience distortions in taste perception. Burning mouth syndrome is also a common complaint. The cause of such dysfunctions is unknown. The prevalence of taste dysfunctions in the elderly is also unknown. Dysgeusia is often associated with dentures, periodontal disease and changes in saliva. The exact mechanism of dysgeusia and its incidence and prevalence in this population are not known.

Some studies have shown replacement of areas of olfactory neuroepithelium with respiratory mucous membrane in the elderly. This finding raises some important questions.

For example, to what extent are the olfactory changes seen with aging attributed to pinching of nerve fibers by the cribriform plate? Does the potential for olfactory cells to regenerate decline with age?

The relationships between chemosensory ability and food preference, appetite and satiety, are poorly understood. They have implications for the nutritional status of the elderly. What are the best ways to assess olfaction and gustation, especially in elderly populations and in demented populations? What is the relationship between psychophysical function and histologic status? Quantitative information on the histology and distribution of normal and abnormal olfactory neuroepithelium is needed. Is the loss of the sense of smell in aging attributable to a defect or loss of first-order neurons or to a lesion in the central olfactory pathways? The answer to this question will require the study of olfactory neuroepithelium through biopsy and the study of the olfactory central nervous system in persons without olfactory disorders of all ages.

Research opportunities include to:

- Study the reasons for variability in the chemosensory performance of the growing elderly population.
- Determine whether the lesions responsible for the olfactory loss in the elderly are in the neuroepithelium or the central olfactory pathways or both.
- Assess the effect of the health status of the elderly on their chemosensory function.

There continues to be considerable interest in the effects of aging on touch. Modern psychophysical techniques permit investigators to examine changes in performance and determine the extent to which they are the result of changes in sensitivity or changes in response bias. The ability to differentiate sensitivity from response bias is particularly important when age is a variable of interest. More needs to be known about changes in touch and particularly the effects of such changes on motor activities, including speech and eating and, more generally, on the quality of life.

Research is needed to:

- Study the effects of aging on touch sensitivity and activities related to touch.

Impact of Chemosensory Disorders on Nutrition, Safety and the Quality of Life

Individuals with a loss or alteration of smell or taste often say that they have lost weight from loss of appetite secondary to their chemosensory change or have gained weight from a stimulation-seeking gain in appetite. The weight gain often comes from a switch of intake to foods with a high fat content. That raises the question of whether there are other nutritional risks associated with chemosensory disorders. Finding the answer requires studies of both controls and individuals with chemosensory disorders.

Individuals with chemosensory disorders do not always share the information about their conditions with others. Individuals sometimes delay seeking treatment until long after the onset of their symptoms and sometimes give up seeking help after a clinician fails to uncover the cause of the symptoms. For these and other reasons, individuals often present at chemosensory clinics with symptoms that began years earlier. Such individuals often exhibit high frustration, intense focus on their symptoms, long-established patterns of ill-advised food intake and altered social and family relations. Parents may, for example, feel incompetent to prepare food for the family.

Although some of the psychological and potential nutritional problems associated with chemosensory disorders may be managed with enlightened patient care, there is considerable room for the generation of research knowledge about effective strategies. Will early intervention, for example, decrease nutritional risks and head off psychosocial disturbances? Are there cultural or gender differences that influence risks? Systematic exploration is required to characterize the psychological changes, such as depression, that occur in individuals who suffer from loss of sensitivity or distortion of function, as well as to characterize the coping strategies used by such individuals. Studies also should explore the similarities with and differences from the changes and coping strategies in other chronic diseases or sensory disorders.

Research on aging has revealed gradual loss of chemosensory function throughout adulthood, particularly after the fifth decade. People often are unaware of their sensory loss. Such gradual and imperceptible changes may also take place in people exposed to environmental and occupational contaminants. Older, chronically exposed workers may therefore fail to appreciate the danger from contaminants that a younger person would avoid. Thresholds for the odors of most industrial contaminants have not been gathered systematically. Often, industrial hygienists rely on odor warning for a worker to notice a contaminant leaking through a respirator. Use of inaccurate threshold values or of values measured on young people can compromise safety in an older person with gradual smell loss. There is a need to discover risk factors for smell loss (for example, susceptibility to loss from industrial exposure to contaminants), to gather data on the distribution of sensitivity to industrial contaminants and perhaps to give people ways of assessing their own sense of smell. The use of odors as gas-warning agents also requires consideration of levels that will protect older people and others whose losses of sensitivity do not lead them to seek medical help.

Research opportunities include the need to:

- Evaluate risks associated with nutritional factors in individuals with chemosensory disorders.
- Identify strategies to prevent and manage the adverse psychological effects of chemosensory dysfunction.
- Determine how chemosensory stimuli act to modulate digestion and utilization of nutrients and whether chemosensory disorders compromise these processes.
- Investigate the interaction between chemosensation and the opioid system.
- Assess the influence of a covert decline in chemosensory function on safety in the home and workplace.

Effects of Occupational, Environmental and Infectious Agents on Function of Smell, Taste and Touch

Smell, taste and oro-nasal trigeminal receptors are in direct contact with the external environment and they are at risk of exposure to potentially harmful infectious or toxic agents.

Although chemical senses alert individuals to environmental chemicals such as pollutants, industrial chemicals in the workplace (vapors and dust) and toxic wastes, such chemicals also may damage these vital senses. Such sensory impairment, particularly in the workplace, contributes to employee absenteeism, loss of productivity and potential litigation. In addition, workers with impaired sensory function are at increased risk (health and safety) of further exposure and harm from deleterious agents. Workers exposed to cadmium, for instance, show a loss of olfactory function.

Research opportunities include those to:

- Develop detectors to protect specific employee populations, such as fire fighters, police, special hazard teams and astronauts.
- Investigate olfactory function in individuals from regions of the country where there is a high concentration of industrial or agricultural toxicants.

Chemical signals released into the environment can exert pronounced physiologic effects on primates, ranging from reduced rates of maturation to suppression of reproduction. Humans commonly live in closed microenvironments, such as air-conditioned buildings. This kind of environment is magnified in a space capsule, where crew members share high concentrations of body volatiles, which may cause both depression and nausea.

Complaints of environmental odors, produced by industrial wastes, municipal disposal systems and other sources, are common. The point at which environmental chemicals become health hazards or cause unreasonable stress is not known. This problem will certainly grow. Although an environmental odor can be recognized as unpleasant, the effects on mood, performance and behavior have had little clinical study. Multidisciplinary studies on defining tolerable levels and health effects of environmental chemicals are critically needed.

Research opportunities include those to:

- Assess the role of pollution and occupational exposure on chemosensory function.
- Identify odorants that modify mood, performance and behavior and determine their mechanisms of action.
- Investigate whether individuals with multiple chemical sensitivities have altered chemical senses.
- Protect and monitor the worker for incipient chemosensory losses attributed to exposure to the occupational environment.

Olfactory receptor neurons provide a direct connection between the external environment and the brain. A vigorous nerve transport system moves substances taken up by olfactory receptor cell bodies in the nose into the olfactory bulb and, in some cases, still further into the brain. A variety of low molecular weight organic chemicals, certain proteins, colloidal gold and pathogens reach the brain by this route. Potentially, the system can provide a route for administration of therapeutic substances to specific targets in the brain, avoiding the blood-brain barrier, which ordinarily prevents such access.

The olfactory nerve also can serve as a pathway for some toxins and pathogens. Herpes simplex virus type I, some neurotropic arboviruses and vesicular stomatitis virus, for instance, are transported into the brain through this pathway. Once in the brain, they can spread extensively. According to one hypothesis, the olfactory sensory deficits expressed in early stages of Alzheimer's disease may be the result of a causative agent that gained entry through these receptor neurons. Studies of this process may have important implications for improvements in public health and for improved neuropharmaceuticals.

Research opportunities include to:

- Investigate the role of the olfactory nerve in the transport of toxins and pathogens to the brain.
- Study the potential of the olfactory nerve for administration of pharmacologically relevant substances to the brain.
- Develop animal models to investigate these processes.

There are several potential occupational and environmental hazards for the sense of touch. Hand and arm vibration syndrome results from prolonged exposure to vibration. Exposure to certain toxic chemicals may lead to loss of tactile sensitivity. Indeed, in some instances the first symptom of exposure may be subtle changes in tactile sensitivity.

Research is needed to:

- Examine the environmental and occupational agents that may affect touch.
- Develop diagnostic tests to determine both normal and abnormal touch sensitivity.

Strategies for the Management of Sensory Disorders, Including Prevention, Treatment and Rehabilitation

Prevention of Chemosensory Disorders

The knowledge necessary for prophylaxis of chemosensory loss is largely lacking. In some cases, antibiotic ingestion in the year before onset of a loss of the sense of smell apparently mitigates the severity of the loss. Likewise, administering conjugated estrogens to postmenopausal women may protect some of them from anosmia and hyposmia. However, the accuracy of these observations needs to be substantiated. The mechanisms underlying sensory loss after radiation and chemotherapy have not been explored adequately. Similarly, medication-induced sensory dysfunctions warrant further exploration.

Research opportunities include to:

- Develop new means of preventing chemosensory losses.
- Examine the unintended consequences of medical and surgical therapy on chemosensory function.

Treatment Strategies for Smell, Taste and Touch Disorders

Smell and Taste Disorders

The loss of the senses of smell and taste may result from impaired stimulus access to the receptors (transport disorders), or from damage to the receptors or their central pathways (sensorineural disorders). Transport disorders in smell and taste can be treated with allergy management: antibiotic therapy; topical and systemic corticosteroid therapy; and with surgery to treat mechanical obstructions, chronic infections, polyps and tumors. In the event of intractable sensory loss, effective strategies to deal with safety, nutritional and quality-of-life consequences must be developed. In special cases, such as individuals who have had a laryngectomy, training in how to get airflow into the nasal olfactory cleft has proved helpful. A device (the larynx bypass), although somewhat cumbersome for everyday use, has proved very effective in providing laryngectomes with an ability to smell.

Currently, there are no therapeutic strategies for the sensorineural disorders of smell and taste. Rehabilitative strategies include psychotherapy, use of devices such as smoke and gas detectors, vigilance regarding potentially spoiled food and the use of flavor enhancers, as well as special textures in foods.

Research is needed to:

- o Design and implement clinical trials of therapeutic strategies for sensorineural disorders of smell and taste.

The existence of progenitor cells in olfactory neuroepithelium that may be multipotential raises the possibility that they are capable of being directed to develop into other neural lineages. The use of molecular biologic techniques and methods of cellular transformation may permit the generation of therapeutic approaches to cellular transplantation to repair chemosensory deficits in both central and peripheral sites. The precursor cells can be envisioned as being derived from fetal tissue or from the individual with the disorder by olfactory biopsy utilizing developments in cell biology.

Research is needed to:

- o Develop diagnostic and therapeutic approaches to chemosensory dysfunction that use advances from molecular biologic, cell and fetal tissue research.

Kallmann syndrome is a human genetic disease associated with anosmia and hypogonadism that is caused by a defect in neural cell migration during prenatal development. The ability to identify and clone the gene for Kallmann syndrome provides new opportunities for diagnosis, treatment and research into basic mechanisms of olfactory development. Individuals with Kallmann syndrome have olfactory deficits as well as endocrine dysfunction. Further work on this syndrome could lead to additional understanding of other genetic defects in olfactory function. In addition, the demonstration of the chromosomal proximity of olfactory marker protein (OMP) and shaker-1 (a hereditary auditory defect) in the mouse, coupled with the synteny of mouse and human chromosomes, suggests that mapping of the OMP locus in humans would give access to a homologous auditory gene defect in humans.

Research is needed to:

- o Develop tests for the prenatal diagnosis of Kallmann syndrome.
- o Evaluate strategies, including gene therapy, for the prevention and treatment of Kallmann syndrome.
- o Create transgenic models to study the basis of olfactory development.
- o Map the chromosomal localization of various olfactory genes to determine whether cross sensory modality gene proximity is a general phenomenon that will

facilitate the cloning of other genes for hereditary defects and provide diagnostic reagents.

- Develop clinical intervention protocols for genetic intervention in individuals with Kallmann syndrome.
- Identify other genetic defects that affect the smell and taste functions.

Touch Disorders

Changes in touch sensitivity may be indicative of an underlying disease state and also may be a problem in their own right. Within the general framework of knowing that a particular condition may produce a loss of touch sensitivity, much more needs to be known concerning the determination of the loss of touch sensitivity or other functions and the range of individual differences in normal and altered touch sensitivity. Practical stimulation and diagnostic techniques need to be brought to bear on the general problem of diagnosing and treating touch disorders.

Research is needed to:

- Investigate the relationship between changes in touch and changes in object manipulation and object identification in populations with diminution of touch sensitivity.
- Develop practical, compact devices to present controlled, complex patterns to the skin.
- Use imaging techniques to measure central nervous system responses to cutaneous stimuli.

Tactile Aids

As noted above, tactile aids have been developed for individuals who are deaf, hard of hearing or blind. Some of these aids have proven useful in aiding persons with hearing impairment to understand speech and to respond to environmental sounds. Improved understanding of hearing and speech and of the sense of touch coupled with improved technology can yield better tactile aids. To deliver these aids to the user population will require close cooperation among a number of specialists.

Research is needed to:

- Encourage cooperative investigations of tactile aids involving rehabilitative specialists, otolaryngologists, engineers, speech scientists and sensory scientists.

VOICE AND VOICE DISORDERS

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VOICE AND VOICE DISORDERS

Overview

Emergence of Voice Science and the Science of Voice Disorders

Voice production (phonation) is the generation and modulation of sound and is a subset of the more global process of speech production. Disorders of voice involve difficulties with pitch, loudness and quality. Voice disorders can be distinguished from articulation disorders, which present difficulties of speech sound production. Many people who have acquired normal speaking skills become communicatively impaired when their vocal apparatus fails. This impairment is important in modern society because there is much demand for effective speech and oral communication.

Additional demands on the voice are made because of negative influences from noise and pollutants in the environment. There are also increasingly larger populations of the aged and hearing-impaired persons and people under psychological and physical stress. Voice production is not the only function of the larynx (voice box). This organ plays a vital role in protecting the tracheobronchial tree, particularly during swallowing.

Within the last decade, the field of voice science has expanded in several ways. A large new knowledge base has been developed on the mechanisms of phonation. Awareness of voice disorders has increased. A clinical delivery system has emerged with improved diagnosis and treatment of individuals with voice impairment, laryngeal pathology and swallowing disorders. These developments have resulted in the need to address research strategies in the voice and speech systems separately.

Interaction of the Voice and Speech Systems and Their Disorders

In the context of communication, voice is an acoustical representation of language. It is a product of laryngeal and upper aerodigestive tract adjustments that act upon and interact with the respiratory airstream to create the physical disturbances we perceive as sounds. The respiratory system, which is an integral part of the voice production system, provides the energy source and must be coordinated with laryngeal valving and upper aerodigestive tract modulation of the respiratory airflow. Vocal tract shaping above the larynx in the hypopharynx, pharynx, nasopharynx, oral cavity and nasal cavities affects the quality of the voice and is also part of the voice-production system.

Speech involves adjustments of the pharynx, tongue, velum (palate), lips and jaw, which modify and enhance the sound source. Articulatory valving and obstructions of the airflow can produce major downward modulations on glottal function. This is only one example of the close interaction between the voice and speech systems. Other significant interactions result from the effects of tongue position on the height of the hyoid bone and larynx during speech.

The same upper aerodigestive tract structures involved in voice and speech production are also required to coordinate the activity of swallowing. Therefore, although normal structure and function and diseases and disorders of the voice, speech systems and swallowing can be studied independently, their interrelations also need to be studied.

Background

The larynx is a valve structure between the trachea (wind pipe) and the pharynx. It has a skeleton consisting of several cartilages, the largest of which is attached to the hyoid bone in the upper part of the neck. Muscles covered with mucous membrane form the vocal folds, which are moved apart to open the larynx or are pulled together for closure.

An important role of the larynx is protection and maintenance of the airway. The vocal folds are separated during inspiration, and air passes into the trachea to the lungs. During expiration, movements of the vocal folds participate in the control of the rate of airflow out of the lungs. During swallowing, the larynx is elevated, moves anteriorly and is closed tightly, while the tongue and pharyngeal muscles move food or fluid into the esophagus. During a cough, the vocal folds close while expiratory muscles contract to increase pressure in the lungs. The larynx opens abruptly, air rushes out and mucus or foreign matter is ejected from the tracheobronchial tree. If the larynx is irritated by particulate matter, reflex closure of the vocal folds and coughing occur. These actions prevent life-threatening aspiration pneumonia.

Voice or phonation is generated by airflow from the lungs as the vocal folds are brought close together. The vocal folds vibrate when air is pushed past them with sufficient pressure. The vibration of the folds causes the airflow to become pulsed. This pulsed airflow is then modulated by aerodigestive tract structures (the pharynx, oral cavity and nasal cavities) to produce the sound that is perceived as voice during speech. Without normal vibration of the vocal folds in the larynx, the sound of speech is absent and words can only be mouthed. They cannot be heard or understood by others, either in face-to-face conversation or over the telephone. To produce a whisper, the vocal folds need to be partially separated, and speech can only be understood by persons very close by.

When vocal fold vibration is impaired, sound generation for speech is affected. An absence of one vocal fold may result in voice loss or impairment. Absence of both vocal folds results in a loss of voice or aphonia. This happens when the larynx is removed, as may be required in laryngeal cancer. Growths on one or both of the vocal folds can change the mechanical properties of the tissue, which affect its vibration. Lesions, such as polyps, result in a hoarse voice caused by irregular vocal fold vibration. Other tissue changes, such as nodules, edema or contact ulcers, can also cause a hoarse voice. Papillomatosis, a spreading of wart-like growths on the vocal folds, also interferes with voice production by limiting vocal fold vibration and the intake of air through the larynx to the lungs.

The nerves controlling the functions of the larynx can be impaired as a result of accidents, surgical procedures or viral infections. When the motor nerves on one side are affected, the muscles moving the vocal fold are paralyzed and the vocal folds cannot come close enough to the center of the larynx. In such individuals, there is excessive air loss between the vocal folds during phonation, which results in a breathy voice. When the nerves on both sides of the larynx are affected, the muscles may not separate the vocal folds properly for breathing. This situation may occur in some motor neuron diseases or following operations on or trauma to the neck.

Both unilateral and bilateral laryngeal nerve paralysis can result in aspiration during swallowing, because laryngeal movement is reduced and the larynx does not close.

Loss of laryngeal sensation can also be a problem. A sensory loss alone can result in food or liquid entering the trachea, and aspiration can cause pneumonia.

The complex functions of the upper aerodigestive tract can be severely impaired by diseases of the central nervous system. Both sensory and motor lesions can significantly impair reflex control as well as voluntary control. Brain stem damage is particularly devastating to swallowing function.

Laryngeal movement disorders have only recently been studied systematically. In spasmodic dysphonia, the muscles of the larynx contract abnormally during speech, causing uncontrolled pitch and voice breaks and sometimes affecting swallowing and breathing. Vocal fold tremor, a disorder attributed to rhythmic contractions of the muscles of the larynx, causes the voice to quaver with frequent pitch and voice breaks. Another disorder, laryngospasm, is an uncontrolled closing of the vocal folds, which interferes with breathing.

Interpersonal stress and psychological factors can have a profound impact on the upper aerodigestive tract. This is not surprising, as the voice directly expresses emotion, and eating is a frequent focus of psychogenic disorders.

Incidence, Prevalence and Impact on Society

Most of the statistics regarding voice disorders are from studies of school-age children. In these populations, estimates of the incidence of voice disorders range from six to 23 percent. The majority of these children have hoarseness, which has resulted from vocal abuse.

There are no data available on the incidence of voice disorders in the general adult population. However, voice disorders are believed to be more common in older adults. Voice and swallowing problems are very frequent in patients with acquired neurogenic diseases.

The economic impact of voice disorders on our society cannot be accurately assessed. However, voice disorders can have devastating effects on individuals, interfering with speech. Often, individuals are unable to function in work situations. Use of the telephone may be impossible without utilizing a telecommunication device for the deaf (TDD) and some individuals are forced to rely on writing for communication. Careers can be lost or limited because of the onset of a voice disorder.

Impairment of respiration or swallowing can be life threatening. Often, the only available treatment results in a loss of voice. When swallowing is severely affected, nonoral feeding is required and the quality of life is diminished.

Recent Accomplishments and the Current State of Research

Normal Structure and Function

Laryngeal Physiology

The biomechanics of laryngeal behaviors that produce different movement trajectories during respiration, airway closure, swallowing, coughing, singing and speech have been studied. Recently, properties of laryngeal muscles have been found to differ from properties of other muscles. Laryngeal muscles are resistant to fatigue, are able to contract rapidly and are less susceptible to injury. Experimental studies have demonstrated the possibility of reinnervation of the laryngeal muscles after neural injury with and without surgical intervention.

Lifespan Changes

Research has revealed specific anatomical, physiological and biochemical alterations with maturation of the upper aerodigestive system. Laryngeal position and configuration change during development and with aging. Swallowing is also affected by aging. Prolongation in oral transit times and delay in initiating the pharyngeal phase of swallowing have been defined in the elderly. Changes in laryngeal muscle contraction behaviors with maturation have also been reported. As well, the cellular biology of the upper aerodigestive system has been found to change with age.

A series of histochemical, ultrastructural and stereological investigations have been initiated on the aging human larynx and its innervation. Studies on animal models have demonstrated a number of changes in morphologic parameters that are likely to play key roles in the mechanisms underlying age-related laryngeal dysfunction. In addition, studies on the human superior laryngeal nerve have shown a large, selective loss of the smallest nerve fibers. This finding may help to explain the age-related dysfunction of the laryngeal protective mechanism.

The use of organotypic cultures to study epithelial-mesenchymal interactions and enhance epithelial differentiation in vitro has been stimulated by advances in dermatology. Application of these techniques to the larynx has provided insight into the plasticity of the adult human laryngeal epithelium. The differentiation pathway into either stratified squamous or ciliated columnar epithelium can be modulated by changing the concentration of retinoic acid in the medium. This understanding raises questions regarding the use of retinoids in chemoprevention of cancer, and it opens potential avenues of research.

Exceptional Behavior

Training of the voice leads to morphological and behavioral changes in the quality and health of the laryngeal tissues. An understanding of these changes can improve the quality and health of the voices of nonprofessionals as well.

Voice training has an important impact on vocal function. Singers have greater frequency and intensity ranges and lower airflows. One consequence of these advances in knowledge is to include singers as a special population in descriptive databases.

There is growing evidence that the voices of trained vocalists change less rapidly with age than those of their nonsinging counterparts. Further study may help develop preventive programs for presbylarynx. In addition, singers appear to be better able to compensate for laryngeal deficits. This finding has implications in voice training for patients with vocal disorders.

Animal Models

Studies are under way to document the role of the central nervous system in the control of laryngeal behavior, vocalization and swallowing. Through the recording of electrical potentials from single neurons in awake, vocalizing animals, the function of various structures is now being understood in the context of the behavior of a normal, healthy animal.

Neural activity has been recorded concomitantly with electromyograms of the upper aerodigestive tract to investigate the integrative actions of the larynx and the rest of the respiratory system in behaviors such as vocalization and swallowing.

Sets of neurons in the periaqueductal gray area of the midbrain have been documented to influence the activity of coordinated groups of neurons to the larynx and the rest of the respiratory system during vocalization. Neurons in the nucleus ambiguus are strongly influenced by cells of the midbrain periaqueductal gray area during vocalization and by cells of the nucleus tractus solitarius and reticular formation during swallowing.

Techniques using multiple arrays of neural recording electrodes have been developed for the study of other systems in awake or anesthetized animals. As the software supporting technology develops, these techniques should yield data on large samples of simultaneously recorded cells and lead to an improved understanding of the functions of specific structures.

Knowledge of the interactions between laryngeal sensory and motor systems has recently been advanced by the development of an animal model that can produce phonation even though the animal is completely anesthetized. This preparation affords researchers the opportunity to study the behavior of laryngeal motor neurons, sensory afferents of the larynx and the mechanisms of how phonatory control interacts with protective reflexes and swallowing.

Anatomy and Physiology of Swallowing

The application of electromyography, endoscopy, manometry and combined techniques (such as videofluoroscopy and manometry combined with computer image analysis) has offered new insights into normal and disordered swallowing. In the past five years, there has been recognition that swallowing is not one behavior but a set of behaviors that vary in their temporal and kinematic characteristics. Some of the factors responsible for systematic variation in swallowing have been identified. These include bolus volume, viscosity and voluntary maneuvers. In particular, the potential for volitional control over laryngeal movement, cricopharyngeal opening and airway closure has been delineated.

The physiology of the upper esophageal sphincter has received special attention relative to the mechanisms of opening and variations with bolus volume. The major elements responsible for opening of the upper esophageal sphincter have been defined as: (1) relaxation of the cricopharyngeal muscle; (2) anterior and vertical laryngeal movement, which opens the sphincter; and (3) bolus pressure, which modulates the width of the opening.

Advances in the Diagnosis and Treatment of Voice Disorders

Vocal Fold Neoplasms

The development of improved visualization of the larynx along with video recordings should lead to improved accuracy in the early diagnosis of laryngeal cancer. When such disorders are detected early, the prognosis for cure while maintaining voice function is good.

Patients can now be fitted with prosthetic devices to redirect airflow and allow voice production soon after surgical removal of the larynx for treatment of laryngeal cancer. Previously, such patients had only two alternatives: to learn esophageal speech or to use a mechanical larynx or electrolarynx. Prostheses provide voice for speech with less training and without an external device. Refinements in design of these prostheses should make speech sound more natural.

Recent advances in the understanding of recurrent respiratory papillomatosis should improve management of this disease and hopefully prevention. The viral cause and latency of the infection are better understood. Quite recently, it was shown that a major contribution to the mass of these tumors is derived from a failure of differentiation rather than increased proliferation. Organotypic tissue cultures mirror this abnormality, thus providing a good model for studying potential modulations of the differentiation process. Interferon cannot eliminate the papilloma virus infection, but it may have a potential adjuvant role in managing patients with severe disease.

Photodynamic therapy using agents that are absorbed by the tumor is currently being evaluated for respiratory papillomas and superficial malignancies.

Vocal Fold Lesions and Glottal Insufficiencies

Phonosurgery is a relatively new specialty that requires skill and new instruments for delicate operations on the vocal folds. Surgical techniques are being designed to improve and restore voice by removing benign growths, correcting structural abnormalities and repairing trauma. Previous common practices such as vocal fold stripping have been found injurious to the voice. Improvements in technique make it easier to restore normal vocal function.

Neurogenic Disorders

Neurogenic Disease

Neurally based laryngeal problems account for a substantial portion of all voice disorders and such disorders are frequently the first signs of neurogenic disease. Recent technological advances have made it possible to view the laryngeal structure and its gross movement patterns, as well as to make fine measurements of moment-to-moment changes in the cycles of vibration. Voice measurement techniques and computational analysis have yielded information delineating voice changes related to the early course of neurogenic diseases. This information may now be used to make earlier identification of some diseases and to allow investigators to have a measure against which to determine the efficacy of treatment.

Laryngeal Paralysis

Unilateral laryngeal paralysis can result in hoarseness and aspiration due to incomplete closure of the glottis. Vocal fold paralysis abolishes abduction and adduction of the vocal folds and alters the configuration of the glottis. The paralyzed vocal fold is shorter than the normal vocal fold and frequently lies at a different level. Compensatory behavior includes hyperadduction of the mobile vocal fold and anterior-posterior compression of the glottis.

Bilateral paralysis is potentially life threatening, because the airway is severely reduced. Established therapy is to perform a tracheotomy, move one vocal fold laterally or excise an arytenoid. Research is being conducted on alternative therapies, such as reinnervation of laryngeal muscles or artificially stimulated laryngeal movement synchronous with breathing.

Many individuals with clinically apparent laryngeal paralysis do not have muscle denervation that can be demonstrated by electromyography. These individuals seem to have partial neural lesions or ineffective neural regeneration. It is now known that recovery from paralysis requires not only regeneration of a sufficient number of motor nerve fibers but also the connection of nerve fibers to appropriate muscle fibers. Synkinesis is the simultaneous contraction of opposing muscles and results from the innervation of muscles by inappropriate nerves. Research into nerve regeneration may elucidate factors that could prevent synkinesis.

Spasmodic Dysphonia

Spasmodic dysphonia is a voice disorder characterized by frequent voice and pitch breaks or a breathy voice. It is a focal dystonia of the larynx. Dysfunction results from involuntary contractions of laryngeal muscles during speech. Surgical division of the nerve to one side of the larynx can diminish the signs and symptoms of adductor spasmodic dysphonia, but the voice is frequently breathy and the long-term results are often not satisfactory.

Several years ago, botulinum toxin was introduced as an experimental treatment. Minute quantities of the toxin are injected into the affected muscles to produce temporary weakness. Recently, a National Institutes of Health consensus development conference judged this approach to be a safe and effective treatment for patients with adductor spasmodic dysphonia. Although it does not cure the disorder, it significantly reduces signs and symptoms, usually for periods of four to six months.

Other Movement Disorders

Movement disorders affecting the larynx, such as false laryngeal asthma or paradoxical movements, have been recognized. Information concerning the effects of these movement disorders on voice and breathing and their remediation is emerging.

Population Considerations

Advances have been made in recognizing that the impact of vocal lesions is population-specific. For example, singers with vocal nodules may compensate sufficiently to mask vocal signs during speech but have difficulties singing. These population differences help explain some discrepancies in the existing literature and underscore the need to look at singers as a special population even when testing for voice disorders.

Gastroesophageal Reflux

Recent studies have elucidated a variety of disorders caused or aggravated by gastroesophageal reflux to the larynx and pharynx. These disorders include contact ulcers, subglottal stenosis, hoarseness, chronic cough, throat clearing and cancer. There is a need to understand more fully the role of acid and alkaline materials in the causes of these disorders.

Technology

There have been advances in computational tools, both hardware and software. Speed, memory, ease of use, cost and compactness have been improved. These developments have affected virtually all aspects of research in the larynx and upper aerodigestive tract.

Analysis and interpretation of signals from electromyographic, electroglottographic, photoglottographic, accelerometric and aerodynamic transducers can now be accomplished with greater accuracy and ease. The use of microprocessors now permits multichannel data acquisition, near real-time quantification and graphic display of complex data. Furthermore, advanced signal processing techniques, in combination with the general availability of digital signal processing boards, have also made it possible to extract interpretative data for scientific and diagnostic purposes in near real time. Improvements in performance and reductions in size and cost have also increased widespread clinical access to the new technologies.

In conjunction with increasing computational capability and transducer design, important progress has been made in imaging and the interactive display of three-dimensional laryngopharyngeal structures. There have been technological advances in videoendoscopy and related digital imaging, magnetic resonance imaging, computed tomography and ultrasound.

Advances in available software make it possible to achieve quantitative evaluation of the images.

These developments have led to intraoperative applications that improve surgical results. Currently, intraoperative monitoring of vocal fold kinematics, electrical stimulation and acoustic output are being used. Further advances in surgical technologies have included the use of endoscopic, fiberoptic, tunable lasers for treatment of disease of the airway.

Augmentative and alternative communication devices and aids are beginning to include an increased variety of synthesized voices with better voice quality. These improvements include the choice of a more natural female or male voice. Further computational analyses and modeling of the human vocal tract should lead to the development of prosthetic devices with even more natural sounding voices.

Program Goals

The program goals for voice and voice disorders are to support research that will enable the acquisition of new knowledge of a fundamental and applied nature that will enhance our understanding of: (1) normal voice and swallowing mechanisms; (2) disordered voice and swallowing mechanisms; (3) evaluation processes for disordered voice and swallowing; and (4) therapeutic interventions for disorders of voice and swallowing. Broad goals include:

- Support epidemiologic studies of the incidence, prevalence and impact of voice disorders, as well as the factors that cause or contribute to vocal dysfunction.
- Foster research that examines the multiple functions of the larynx and upper aerodigestive tract in an integrated manner.
- Encourage multidisciplinary research that studies interactions of molecular, cellular and organ systems within whole organisms.
- Encourage studies of the efficacy and relevance of new technologies, procedures and treatments.
- Support acquisition of a database that permits the evolution of standards for documentation of vocal function.
- Facilitate training of scientists to study voice, voice disorders, swallowing and swallowing disorders.

Research Opportunities, Strategies and Priorities

Normal Structure and Function

Knowledge of normal structure and function is an important basis for understanding the voice and its disorders. Voice is produced by a unitary system consisting of functional subsystems -- respiratory, laryngeal and upper aerodigestive. It is important to understand how these subsystems act and interact with one another and to know the principles that govern the overall system's potential to reorganize and adjust its behavior. Such information is also relevant to understanding both the adaptive and maladaptive behaviors of the voice-producing mechanism in response to laryngeal disorders or diseases.

To be relatively comprehensive, the knowledge base about voice and its disorders should include data from several domains, such as the neural, muscular, structural, aeromechanical, acoustical and perceptual domains. It is also important to relate such knowledge to specific functions and forms of expression, including those that are psycholinguistic and artistic.

Laryngeal Function in Vocalization, Respiration and Swallowing

The use of common spatial and relational references should make it possible to use multivariate data to support the comprehensive modeling of laryngeal function and dysfunction. Studies are needed on a wide range of parameters to facilitate the integration of multivariate data from various research groups using different techniques. Contributions to this database should include information on morphology, physiology, molecular biology, cellular biology, biochemistry, histochemistry, immunocytochemistry, biomechanics, age, gender, cultural background and lifestyle.

Emerging techniques make it possible to study the neural control of the larynx in vocalization, respiration and swallowing in humans and animals. Such studies should address the ways in which the nervous system integrates the control of these behaviors autonomously and in response to changes in sensory inputs to the nervous system. Additional work needs to be done on defining mechanisms in terms of receptor type and pathways for the cough, gag and swallow reflexes.

There is a need to delineate the effects of sensory input from bolus characteristics, respiratory parameters and voluntary control on timing, the extent of laryngeal elevation and closure and pharyngeal contraction during swallowing.

Recently developed noninvasive techniques, such as transcranial magnetic stimulation and sensory evoked potentials, offer new opportunities for research on humans. These techniques can be used for mapping the cortical control of the larynx.

Electrical stimulation of the recurrent nerve can elicit short- and long-latency reflexes and provide new insights into the on-line modifications of activity of the brain stem motor neuron pool during different phases of respiration, phonation and swallowing.

Biomechanics of the Larynx

To understand how vocal pitch and loudness and voice quality are controlled, it is important to study the mechanism by which the laryngeal and respiratory muscles move tissue and air. Study of the effectiveness of muscle groups working in concert is needed. The importance of the lubricating fluids on the vibratory behavior of the vocal folds is recognized, and further study is needed of the composition and aberrations of this fluid layer.

The biomechanics of complex laryngeal structures and material properties, which formerly posed many problems for quantitative analysis, can now be addressed by finite element and other computational means. In other fields of biomechanics, the mechanical properties of skin, cartilage, fat, ligament, tendon and muscle have been studied extensively. The results give voice scientists a rich database for comparisons. The combination of new analytic tools and new databases makes the biomechanics of the larynx an attractive area of investigation. Progress in this area should lay the groundwork for simulation of reconstructive and augmentative clinical procedures.

Studies of laryngeal movement and closure in relation to movements of the hyoid bone, pharyngeal wall and tongue base during swallowing in healthy adults of various ages can contribute to our understanding of normal bolus propulsion and airway closure mechanisms.

Cellular and Molecular Biology and Anatomy

Normal laryngeal anatomical studies are needed in many species, including human postmortem specimens, on light microscopic and ultrastructural levels. These studies would provide an opportunity to define the distribution of extracellular matrix molecules, oncogene expression, growth factors (for example, epithelial growth factor) and growth-factor receptors as they relate to normal structure of the larynx. Organotypic cultures would permit the study of the effects of modulating these components. This research could be done through changes in culture conditions, such as hormone additions and altered matrix components or through insertion of genes into cells that would express growth-factor receptors, etc.

Animal models should be studied to determine their similarities to and differences from the cellular structure of the human larynx. Transgenic animals could be used to define and dissect interactions of multiple components at molecular function and anatomic levels. Shifts in the relation of these components have been implicated both in disease processes and in wound healing.

There have been few studies addressing the cellular and molecular mechanisms of the central nervous system in the control of the larynx for vocalization and swallowing. Descriptive studies are needed to establish the baselines from which various neurogenic disorders affecting laryngeal function can be understood. Studies are needed on the biochemical and structural specializations characteristic of laryngeal muscle fibers and their innervation.

Quantitative, three-dimensional, geometrically referenced anatomical, cellular and biochemical studies are needed in all of the above areas.

Control of Pitch, Loudness, Register and Vocal Quality

Over the past decade, functional models have enhanced the available knowledge of the dynamic behavior of the vocal folds. Electromyographic studies have increased understanding of the role of the extrinsic and intrinsic laryngeal muscles in the control of pitch. The results of these studies have suffered, however, from the small populations sampled and from individual variations. Systematic work on the control of pitch, loudness, register and quality should be continued.

Concentrated work is needed on the role and interactions of specific muscles and of their aerodynamic effects in relation to changes in the length, shape, configuration and forces of the vibrating structures. Studies should consider laryngeal function and the interaction of the larynx with the dynamics of the entire upper aerodigestive tract. In addition, work in this area should be extended to include subject populations other than those studied to this point. Attention should also be devoted to control mechanisms in the singing voice. There is a need to delineate the acoustic to perceptual transform in voice-quality disorders. Advances in signal analysis, control and synthesis, combined with psychophysical procedures, make the time ripe to gather information that would be of use in determining those aspects of the voice signal that give rise to the perception of disorder and its quantities. Age, gender and cultural variables warrant attention.

Vocal Tract Component Interactions

The interactions among phonation, respiration, swallowing and articulation are important. Research should stress the role of the respiratory system as an energy source for the voice. Further study should be given to acoustics and biomechanical interactions, particularly the effects of vertical movements of the larynx and source-filter effects related to adjustments in the pharynx. Additional demands such as increased loudness may bring additional loads to the system. Although such demands have been studied, they must be more clearly defined for different types of vocalization as in whispering, breathy phonation or as a coping strategy accompanying a disease state. In addition, the role of changes of supraglottic and subglottic acoustic and aerodynamic pressures in vocal function and training could be better understood if the neural sensors that help control the process were more clearly defined.

The dynamic behavior of the larynx and its role as an articulator in speech need further attention. Studies focused on the control of timing of laryngeal behavior in coordination with respiratory and articulatory activity may shed considerable light on communication disorders. Interactions between timing and pattern of laryngeal movements during swallowing, as a result of oral sensory input and depending on the respiratory status, are important but poorly understood and deserve further study.

Role of the Larynx and Pharynx in Swallowing

The control of the larynx and pharynx in the swallowing process deserves further study. The systematic effects of sensory input from bolus variables are beginning to be understood. More research is needed on the effects of systematic changes in laryngeal and pharyngeal function during swallowing on various bolus types and on using various voluntary controls. This research has implications for the evaluation and treatment of individuals with dysphagia. Studies of peripheral and central mechanisms controlling laryngeal and pharyngeal transitions among respiration, swallowing and phonation are also relevant to the management of dysphagia.

The Use of Animal Models

Much of the information currently available on the neural control of the larynx has come from animal studies. Attention should be given to the similarities and possible differences in human laryngeal physiology to that of other species proposed as models for human voice production and swallowing. This research is fundamental to an understanding of developmental structure and function.

The use of multiple electrode arrays for the recording of small populations of neurons in the brains of animals should be used to define neural mechanisms of laryngeal control. This technique should lead to more rapid development of models of the neural control of specific behaviors.

Electrically or chemically elicited phonation from the periaqueductal gray area of the midbrain or its immediate surroundings in anesthetized animals should be used to study the function of laryngeal motoneurons, sensory afferents of the larynx and the mechanisms of how phonatory control interacts with protective reflexes and swallowing. This animal model may also be used for experimental manipulation of laryngeal biomechanics and studies of the effects of tissue alterations.

Information gained from the anesthetized animal needs to be tested in the awake, vocalizing or swallowing animal. Only in the awake animal can the interactions among all structures of the upper aerodigestive tract be studied during normal vocalization, swallowing and respiration. The use of chronic single or multiple neuronal recordings combined with voice, electromyography and pressure recordings should be expanded to learn how the central nervous system controls the complex interactions of the larynx during vocalization and swallowing.

Development

The development of vocalization and swallowing, gender differences in these functions and their aging are fertile areas of study. Detailed comparative descriptions are needed that could be used to facilitate the selection of models appropriate to human function.

Embryology

Current knowledge consists of a series of well-defined, descriptive reports of different stages of laryngeal development in several species, including humans. Precursors of the larynx consist of two cell populations, epithelial and mesenchymal elements that interact continuously during development. The mechanisms of epithelial-mesenchymal tissue interactions that are driving forces in the normal development of the larynx and the way that these interactions affect cell differentiation and final organotypic form require study. The understanding of the embryology of this unique organ, therefore, is still quite limited as is the understanding of the repair processes in the injured larynx. Attention should be directed to the study of the anatomic and physiologic effects of operations on the infantile larynx.

Critical Periods

Critical periods for optimum development of vocal control, as well as periods when a speaker may be at risk for developing dysphonia, have been recognized, but they have not been adequately studied. The critical periods that are particularly important for the prevention and treatment of voice disorders include infancy, childhood, puberty and other life cycle stages characterized by hormonal changes. The development of hearing impairment or subjection to a noisy environment at any time may produce critical periods for the development of voice disorders.

- *Infancy*: A time when there are many unique structural and functional changes occurring in this highly specialized system, and the infant is experimenting with vocal controls during playful or demanding vocalization, often at loud levels for long durations.

- *Children*: A time when communicating out of doors over large distances and athletic competition place demands on the voice that may result in misuse and abuse. Alteration of pitch, particularly by boys, increases the chance of voice disorders.

- *Puberty*: A time when there is rapid growth in the larynx resulting in vocal fold lengthening with perhaps insufficient time to allow for proper mechanism adaptation. That this adaptation is not always done readily results in abnormal attempts to maintain the higher childlike voice at the expense of vocal strain and poor vocal quality. These vocal characteristics may result in unwanted attention and have a major effect on the psychosocial development of the speaker.

- *Hormonal changes*: Times when masculinizing tumors or male hormone therapy, pregnancy or menopause result in edematous changes in the larynx. Studies are needed to determine the time periods during which the problem is reversible. Research is needed to understand the role of androgenic hormones and how their effects can be prevented or ameliorated.

Vocal Control

Research studies are needed to characterize voice production as it relates to the developing structure. A major concern is the control of pitch, loudness, register and voice quality with changes in structure of the larynx. Knowledge of normal structure and function in relation to age is requisite for understanding voice production, for developing standards of tests for the early detection of disorders and for determining the efficacy of various forms of treatment. This information is also valuable in developing theoretical models of the cause of voice disorders.

Effects of Hearing Impairment on Developmental Vocal Control

Individuals with congenital and later-onset hearing impairment may have disorders of pitch and loudness control, as well as distinctive abnormalities in voice quality. Only limited attention has been given to the critical periods for the habilitation and rehabilitation of vocal control in these populations. Attention needs to be given to the use of biofeedback and motor learning in training vocal control in hearing-impaired persons.

The effect of cochlear implantation on voice quality in the prelingually and postlingually deaf persons should also be studied further.

Vascular Function

The circulation of blood and its autonomic control in the larynx and the possible relationships to biomechanical changes, vocal fatigue and laryngeal lesions require study. Further research is needed on the relation between circulatory changes and the function of the upper aerodigestive tract.

Aging

Preliminary observations indicate that some of the vocal alterations that have been ascribed to aging are perhaps not attributable to irreversible physiologic or anatomic changes. More research is needed to establish the true nature of aging voice and swallowing changes and to develop techniques to forestall or prevent these changes when they may interfere with a person's life or livelihood. In addition, irreversible changes need to be understood in depth. Study populations should include normal speakers, octogenarians, nonagenarians, centenarians and special populations of voice users, such as singers.

Cell Death

The selective neuronal death in the brain stem as a consequence of aging should be studied. Study of this problem may provide important insights into understanding changes in voice control, respiratory function, reduced airway protection and bolus propulsion in older persons. In some neurogenic diseases, selective reduction in motoneuron pools that modulate speech and breathing have recently been found. Research is needed to determine the degree to which selective cell death due to aging adversely affects voice, swallowing and respiration.

Anatomy and Cellular and Molecular Biology

The anatomy of the aging larynx has been described in human specimens obtained primarily from cadavers. There has been no detailed study of the aging process in other species in which a more uniform genetic background is possible. It would be very useful to collect molecular, cellular and anatomic information from aged larynges of a genetically defined species. Information is needed on the localization of extracellular matrix components, growth factors, oncogene expression and growth-factor receptors. This information should be compared with the data collected from normal young adult larynges and related to the reduced ability of the larynx and pharynx to recover from injury with aging and the increased susceptibility of the pharynx and larynx to general weakness and dysfunction when an elderly individual becomes debilitated.

Muscle Atrophy

It is known that muscle tissue gradually degenerates with age. This process involves an age-related cell death of motoneurons with subsequent reinnervation of denervated muscle fibers by the surviving motoneurons. Because this mechanism can alter the number of muscle fibers innervated by each of the surviving motoneurons, this remodeling process can contribute to age-related changes in motor control. In addition, the muscle fibers may undergo age-related atrophy, hypertrophy or cell death, which may be specific to the muscle fiber type. These changes can differ among types of skeletal muscles and should be important in determining the basic pathogenic mechanisms underlying age-related degenerative processes in the highly-specialized muscles of the larynx and upper aerodigestive systems. Because such changes are likely to be reflected in diminished capacities for vocalization, swallowing and respiratory function of the upper aerodigestive systems, the functional consequences of muscle atrophy should be an area of investigation.

Deterioration of Joints, Ligaments, Membranes and Other Tissues of the Laryngeal, Pulmonary and Secretory Systems

Vocal deterioration or swallowing disorders may result from restrictions in the movement of the glottal structures, as well as from reductions in lubrication. Specifically, the cricoary-tenoid joint, which subserves vocal fold abduction and adduction capabilities, tends to lose the freedom of movement because the capsule of the joint deteriorates. Changes in articular cartilage with thinning and irregularities of the articular surface have been noted with age. Further arthritic changes can result in a joint that is fixed. Little is known about the biology of this process. To correct these changes by means other than surgery, more information is needed on the cellular biology of cartilage and joint deterioration as it affects voice production and swallowing in the aging larynx. This knowledge might lead to medical or exercise therapy to help arrest or reverse the process.

Stiffness and lack of elasticity limit the pliability of the aging larynx. This state affects the membranous cover, which results in less motion of the mucosal wave. With vocal stress, the vocal mechanism is less resilient. The mechanisms involved warrant further research.

Atrophy of mucus-producing glands with aging can lead to changes in the fluid layer of the vocal folds, making clear phonation more difficult. Research is needed to determine how to improve the secretory process leading to increased laryngeal efficiency.

Exceptional (Trained) Vocal Behavior

The larynx is an inefficient sound source in normal conversational speech. Typically, less than one percent of the aerodynamic power of the lungs is converted to acoustic power in speech. As a result, the system might optimize itself for criteria other than efficient phonation. Undesirable vocal habits may be formed in various developmental stages.

When people with poor vocal habits are thrust into situations that require prolonged periods of vocalization, especially with high intensity under high psychological or physical stress, the loss of efficiency takes its toll. Vocally trained people (singers, actors and public speakers) have learned to overcome some of these problems.

The gifted or exceptional vocalist, either in speaking or singing, offers a very important model for the vocal evaluation of all voice users. The model establishes the limits of capability. In pitch control especially, it allows one to see what can be done with respect to range. This information can be used in the average-voice evaluation as a criterion. The same approach is applicable with respect to loudness. Questions of interest are:

How far can the human voice be pushed without strain? What are its limits?

Answers to these questions could lead to better care of people who have deficient usage.

What is the basis for limited efficiency? Is it genetic? How is optimal efficiency achieved?

How does the optimal user gain a greater range of pitch or loudness?

The answers to these questions could lead to better care of a person with a narrow vocal range and low power. The results of the study of pitch, loudness and vocal quality control of this population should help to remediate vocal disorders, particularly in the direction of modifying behavior.

Gender

Gender differences in vocal production are currently under investigation. Research has shown that alterations in estrogen and progesterone levels cause cytologic and physiologic changes in the vocal folds. Reinke's edema has been shown to have an increased incidence in post menopausal women. There is a need for research into the sites of hormonal influence, as well as hormonally affected changes in voice production.

Glottal configuration differences have been noted between males and females and deserve further investigation.

Lifestyle

Little is known about the effects of lifestyle (diet, smoking, drug use, exercise and alcohol consumption) on function of the larynx and upper aerodigestive tract. Study of these variables would enhance knowledge of fundamental mechanisms, including maladaptive behaviors that contribute to the development of disorders. Resulting data would also facilitate the design of prevention programs and early identification of dysfunction.

Diseases and Disorders of the Larynx and Upper Aerodigestive Tract

Diseases and disorders of the larynx and upper aerodigestive tract involve a complex physiologic system and affect functions of voice, respiration and swallowing. Although these problems are often grouped according to etiology, many are multifactorial in origin. For example, vocal fatigue may result from stress, structural abnormalities, neuromuscular dysfunction and environmental factors. Hoarseness may result from the combined effects of allergy and vocal abuse. Dysphagia may also result from multiple causes.

Research into the problems listed below should include both focused studies of specific factors, as well as multidisciplinary investigations. Understanding may be enhanced by the synthesis of knowledge in two conceptual dimensions. A disorder may have an impact on multiple levels in the cell-tissue-organ system, and a single problem may be the result of multiple causes.

Studies should not necessarily be limited to the analysis of specific anatomic or physiologic disorders. When appropriate, issues relating to gender, race and cultural differences should be considered. Outcome studies may shed light on causes, as well as strategies of prevention.

Epidemiology

Disorders of voice are increasingly recognized as a major health problem among persons of all ages and in all walks of life. The causes of voice problems are diverse and, in many instances, unknown. Despite recognition of the devastating effects of voice problems, there are no reliable data on the prevalence of voice disorders among any postpubescent population. Prevalence data are necessary for the adequate planning of health services.

Structural Lesions

Congenital and Acquired Diseases of the Larynx and Upper Aerodigestive Tract

Congenital and acquired lesions result in dysfunction in thousands of infants and children each year. These disorders include cysts, webs or scar tissue or they may result from failure of normal development. Developmental failure can result from interruption of epithelial-mesenchymal tissue interactions during organogenesis. Presently no animal models exist to aid investigators in the study of these problems. The differentiation of genetic and environmentally induced laryngeal and pharyngeal anomalies is important. Understanding the mechanisms of these disorders should lead to improved treatment and perhaps prevention.

Inflammatory and Infectious Diseases of the Larynx and Upper Aerodigestive Tract

Research is needed to improve the understanding of inflammatory diseases of the larynx and upper aerodigestive tract. Rhinitis, sinusitis and laryngitis affect a high percentage of the population, and they cause hoarseness and dysphagia and range in severity from local irritation to irreversible tissue damage. The results of research on prevention, early detection and intervention should help to limit the effects of these diseases. Newer endoscopic sinus surgical techniques appear to represent an important technical advance, but studies are needed to reduce the associated complication rates and enhance long-term therapeutic benefits. Research designed to produce new medical treatments for infectious and allergic disorders is also needed.

Laryngeal papillomas are caused by an infectious virus. A clearer understanding of the biology of the disease would help to determine the therapeutic approach. Long-term research should assess the recurrence rate, the effects of treatment, the effects of cofactors such as smoking and voice abuse and the rates of association with carcinoma of the larynx.

Tumors of the Larynx and Upper Aerodigestive Tract

Neoplasms (new growths or tumors) of the larynx, pharynx, oral cavity and neck may result in loss or serious impairment of the ability to communicate with others. Benign tumors such as recurrent laryngeal papillomatosis may require multiple surgical (usually laser) excisions from the vocal fold region. Postoperative scarring may lead to permanent hoarseness, and failure to control the papillomas may result in death. Studies are needed on prevention, early detection methods and improved medical, immunological and surgical treatments.

Malignant neoplasms involving the larynx and other head and neck structures affect more than 50,000 Americans each year. Cancer in these structures is usually related to the use of tobacco and alcohol, and research is needed into more effective cessation strategies. Early diagnosis often permits the use of radiation therapy or limited surgical excision, such as partial laryngectomy or partial glossectomy. Although the conservative operations maintain most of the functions of speech, respiration and swallowing, more precise data are needed on the long-term deficits that are produced and on strategies to rehabilitate patients. Standardized, prospective clinical investigation and the collaboration of surgeons and speech scientists should be expanded in this area.

Laryngeal transplantation in patients requiring total laryngectomy remains an intriguing rehabilitation possibility. Major obstacles such as appropriate reinnervation of abductor and adductor muscles, as well as problems associated with cancer immunology, remain to be overcome.

Effects of Therapeutic Irradiation on Laryngeal Functions

Approximately 50 to 75 percent of all head and neck cancer patients in the United States presently receive radiation as part of the treatment for their malignancy. It is generally in the form of either definitive radiation alone or postoperative radiation following removal of the gross tumor. There is relatively little information available regarding the effects of irradiation on laryngeal function. With the advent of advanced techniques for laryngeal study, measurements of vocal fold vibration and analysis of acoustic parameters, the opportunities for more objective analysis of radiation effects on the larynx now exist.

In the last ten years, it has become clear that hyperfractionation (multiple small fractions per day) radiation therapy is providing higher cure rates and diminished late normal tissue toxicities. This approach warrants further study.

Increasing numbers of cancer patients are undergoing organ preservation therapies, as opposed to ablation. This means that increasing numbers of patients will be maintaining organs such as the larynx following curative cancer therapy. Thus, increased efforts directed toward understanding the tumor-induced and treatment-induced abnormalities produced in organs such as the larynx should become as important as rehabilitating the postlaryngectomy patient. The impact on vocal function of endoscopic excision or irradiation of early vocal fold cancer should be systematically compared, as this information should be a major factor in selecting treatment.

Screening of High-Risk Patients for Laryngeal Cancer

High-risk patients, that is, those over the age of 50 years with a history of smoking more than 30 packs of cigarettes per year, may represent a select population for laryngeal cancer screening. The combination of indirect examination and videostroboscopic or acoustic analysis may provide a route for identifying cancers at an earlier clinical state. A screening process requires careful design so that it has relatively high sensitivity and specificity and moderate cost.

Effects of Chemopreventative Agents on Laryngeal Function

The era of chemoprevention for head and neck malignancies is well under way. Thousands of patients are now being entered on chemoprevention protocols following curative therapy for a primary head and neck cancer in an attempt to diminish the likelihood of their developing a second one. The effects of these chemopreventative agents on laryngeal function is unknown. Since head and neck cancer is a select site for chemoprevention studies at this time, the effects of these agents on laryngeal function is deserving of study.

Trauma

Injury to the larynx, trachea and upper aerodigestive tract is an increasing and difficult management problem. Both blunt and penetrating injuries can result in serious functional disorders. Further studies are needed to determine the structural and functional sequelae requiring repair and rehabilitation.

Neural Lesions

Central

Control of laryngeal functions for breathing, voice and swallowing is impaired in many neurogenic disorders such as Parkinson's disease, amyotrophic lateral sclerosis, multiple systems disease (Shy-Drager syndrome), Huntington's chorea and stroke. A better understanding of the pathophysiology of these motor control disorders would lead to more effective management (medical, surgical, behavioral or prosthetic) to support speech, respiration and swallowing. Studies are needed to provide information about neuropharmacological and behavioral management of disorders of laryngeal motor control.

Research is needed to clarify the relation between neuropathology and pharyngeal disorders. Information about characteristics of different neurogenic disorders and disease progression is lacking.

Focal dystonias of the head and neck cause disruption of speaking and swallowing and impair the quality of life. Recent advances have been made in understanding dystonias, such as spasmodic dysphonia. Evidence from brain imaging and autopsy studies suggests that dystonias are due to brain lesions or biochemical changes in the basal ganglia. Epidemiologic and case-control studies are needed to identify possible causative factors leading to the onset of this disorder.

New treatment has been developed that uses botulinum toxin injections into the laryngeal muscles to reduce abnormal patterns of laryngeal muscle activation. The optimal dose and placement of injection vary greatly among patients. Research is needed to predict optimal dose magnitude and placement. Preliminary data suggest that the injection of succinylcholine or other agents may be of predictive value. Long-term evaluation of this treatment is needed to determine whether the toxin continues to be effective with repeated injections over several years. Information is needed on the diffusion of the toxin in tissue, distant effects and possible retrograde transport to the brain stem. There is a need to investigate alternative toxins and to learn what the response of spasmodic dysphonia to botulinum toxin tells us about the pathophysiology of dystonias.

Respiratory dyskinesia is a problem that has recently been identified as a separate entity, sometimes associated with asthma. It presents an interesting opportunity for investigation because some patients can be successfully managed using anticholinergic drugs.

Peripheral

Peripheral nerve injuries may affect the larynx and upper aerodigestive tract. One of the most common injuries is to the recurrent laryngeal nerve which results in vocal fold paralysis. This injury occurs most frequently during operations on the skull base, neck or mediastinum. Tumors or infections along the path of the vagus nerve can also interrupt laryngeal function, producing alterations of phonation, airway protection and respiration. In bilateral paralysis, the consequences are often devastating. To date, observations about the effects of laryngeal reinervation remain controversial. Accumulation of a database will improve the ability to diagnose accurately and treat effectively these life-threatening conditions. Clinical trials are required to assess existing and new surgical procedures, including vocal fold augmentation, thyroplasty, arytenoidectomy, cordectomy, selective reinnervation and electrical pacing. Nerve regeneration studies are needed to understand the pathogenesis and to develop new forms of treatment.

Systemic Disorders Affecting the Larynx and Upper Aerodigestive Tract

Endocrine

There has been considerable interest in the effect of hormones on the voice. Imbalances of these biochemicals have a potent impact upon the distribution of electrolytes and water within the extracellular compartments of the vocal folds, causing them to become edematous or swollen and changing the characteristics of their vibrations. These changes occur during hypothyroidism, premenstrual syndrome, androgenic hormone-producing ovarian tumors, pregnancy, and puberty in boys. They may follow the administration of birth control pills and postmenopausal hormone therapy in women. Studies are needed to clarify the best strategies for evaluating and treating these patients and to find new strategies for prevention. In addition, epidemiologic studies, standardization of clinical assessment and a coordinated effort to establish and define clearly a database in this area are needed.

Pharmacologic

Pharmacologic agents can have important effects on the voice. For example, some blood pressure medications cause severe coughing. Other agents that decrease secretions can impair the voice. Anecdotal evidence implicates anti-inflammatory agents or topical corticosteroid sprays in the pathogenesis of vocal fold polyps. There is little research on the effects of drugs on the voice or on the interaction of drugs with other vocal therapy, such as surgery or behavioral management. With an aging population taking increasing quantities of medication, further research is needed.

Psychogenic Disorders of the Larynx and Upper Aerodigestive Tract

Psychogenic disorders of the larynx and upper aerodigestive tract occur frequently but are not well understood. They may be a primary disorder or secondary to a loss of communication skills. It is often difficult to distinguish a psychogenic problem from an idiopathic organic disorder. Research is needed to permit clinical identification of the psychogenic component and to determine how psychologic factors influence treatment outcome.

Wound Healing

Wound healing after injury of or operation on the larynx can have a profound effect on the functional recovery of this generator of sound. New research advances demonstrate the role that some extracellular matrix proteins, for instance, fibronectin and its integrin receptor molecule, play in the improvement of the quality of wound healing. Myofibroblasts have been implicated in scarring and contracture of healing wounds.

At present, knowledge is limited on the role of extracellular matrix, growth factors and oncogenes in wound healing in the larynx. Studies of these factors in wound healing in the injured larynx of animal models are essential to the design of future experiments, in which specific treatments may be assessed that could reduce the negative effect that wound healing has on functional recovery.

The various strategies used in clinical practice to control or influence wound healing should be defined more clearly. There is lack of standardization in dilatation techniques, the timing of procedures and the use of stents to support the airway during healing. Basic information is needed on the pathophysiology, prevention, assessment and treatment of problems associated with laryngeal surgery and injury.

Misuse and Abuse Disorders

Many people have voice misuse and abuse disorders that are attributed to abnormal patterns of phonation. These problems include vocal nodules, chronic laryngitis, hemorrhage into and polypoid degeneration of the vocal fold and vocal fatigue. Suspected contributing factors include excessive loudness and duration, inappropriate pitch, faulty patterns of muscle activation, speaking in noisy or dry environments, chronic coughs and throat clearing. Additional studies are needed to identify epidemiologic factors including prevalence and establish efficacy of treatment. This knowledge should help in the development of preventive measures.

Influencing Variables

Gender

Male and female voices differ acoustically, and there are clear gender differences in laryngeal anatomy. The male larynx is larger than the female larynx, and the configuration is different.

The menstrual cycle and pregnancy affect the nose and larynx and possibly the neural control of phonation. Therefore, it is not surprising that women are more susceptible than men to many voice disorders, including vocal nodules, spasmodic dysphonia and edema of Reinke's space. Vocal fold edema and increased risk of hemorrhage have been observed during menses. On the other hand, contact granuloma is more often observed in men. Research is needed to determine reasons for gender differences in susceptibility to improve prevention and treatment.

Vocal health is also affected by social and cultural factors that affect men and women differently. Bulimia, which is chiefly a disease of young women, may damage the larynx. Many jobs typically associated with women, such as teaching and aerobics instruction, result in vocal stress. Society places vocal role expectations on both genders, that can result in the affectation of inappropriate pitch or vocal quality.

Aging

There is a continued need to study the effects of aging on voice production. Research is needed to understand the mechanism of change and how its effects can be prevented and treated. Preliminary observations indicate that some of the vocal alterations, such as diminution of power and endurance, that have been ascribed to aging may be delayed or reversed through physical or singing exercises. Some alterations may also be attributed to diseases of other systems. Additional research is needed to establish the true nature of age-related voice changes and to develop techniques to forestall or prevent them. There is a need to study such factors as physical health, mental health, nutrition, muscle atrophy, long-term vocal abuse, deterioration of the respiratory system and vocal hygiene and exercises.

Respiratory Tract Factors

The lower respiratory tract is an important, integral element in the production of the acoustical basis for speech. Although a variety of diseases and disorders of the lower respiratory tract affect the voice, detailed analyses of their effects on the voice are needed.

Influence of Environmental Factors on Voice Production

Environmental factors are thought to cause or perpetuate voice disorders. Noise, air pollution and relative humidity are factors that singularly or in combination may cause or maintain a particular disorder. Aspects of voice production that are improved or deteriorate with environmental changes warrant investigation. Understanding these relationships may help in the development of voice treatment and prevention programs.

Racial Factors

Studies have demonstrated clear anatomic differences among races in the size and shape of the skull and facial bones, which influence vocal resonance. Currently, there are no data on whether there are racial differences in laryngeal structure which could predispose different incidences of diseases or disorders. Research is needed to explore these possibilities.

Cultural Factors

Different languages and dialects, as well as social strata, place different demands on the vocal apparatus. Comparative studies may illuminate the incidence and prevalence as well as occupational factors in the pathogenesis of some disorders.

Gastroesophageal Reflux

Gastroesophageal reflux commonly affects the larynx and upper aerodigestive tract. Signs of gastroesophageal reflux include hoarseness, chronic cough, throat clearing and contact ulcers. Further studies are needed to elucidate the relative importance of the acid and alkaline components of gastroesophageal reflux.

Other Disorders

Recent advances in medical technology have produced a growing population of children with chronic illness who require prolonged airway management. Long-term tracheostomies have been shown in the canine model to produce anatomic and physiologic alterations of the airway. Further research should be undertaken to investigate voice disorders in children who have had long-term tracheostomies.

Little is known about genetic influences on laryngeal function and dysfunction. Studies in this area are essential.

Technology

Diagnostic and Treatment Aids

Progress has been made in the development of new research tools for the observation and measurement of voice production. Systematic investigation of electromyographic, kinematic, acoustic, aeromechanical and imaging diagnostic aids should be continued to determine which technique or combination of techniques is most useful for detecting disorders, documenting changes resulting from treatment, identifying persons at risk for developing voice disorders, setting standards for routine assessment and improving the understanding of the process of voice production.

Definition of testing procedures varies from center to center and standards need to be established for voice assessment. It is essential for research and clinical purposes to establish valid, reliable and standardized methods for objective voice assessment, including at a minimum vibratory, acoustic, aeromechanical, electroglottographic and psychoacoustic measures.

More extensive normative studies are needed for the general population, including its cultural diversity, and for professional speakers and professional singers. Age and gender variables should be considered in all groups. In addition, data from the entire range of human vocal responses should be studied in communicative context. Finally, technology from allied fields should continue to be integrated into emerging voice technologies.

Electromyography

The observation of electrical activity in intrinsic and extrinsic laryngeal muscles of normal volunteers and patients with voice disorders is being performed in numerous laboratories. The results have been used in an attempt to understand the basis of normal speech processes, as well as to help in the diagnosis of voice disorders. Although it seems clear that electromyographic recording has great potential for contributing to the understanding and treatment of voice disorders, several issues require attention. Currently, there is neither uniformity among the techniques that are used nor consensus on voice disorders in which these techniques have a high probability of being useful diagnostic procedures. Further research is needed to address variations in electrode configuration, interaction of the electrode with the muscle, verification of electrode placement and testing procedures.

Collaboration among experienced electromyographers, voice scientists and physicians with specific knowledge of laryngeal anatomy and diseases is important. Reporting of electric potentials in standardized units and methods should enable comparison of observations from different laboratories. Nonvoluntary activation of laryngeal nerves, by electrodes or magnetic stimulation, offers opportunities to verify the integrity of laryngeal nerves in infants or anesthetized patients.

Acoustic Signal Analysis

Recently, manufacturers have begun to offer a wide variety of relatively low-cost, acoustic analysis devices designed to provide quantitative information on voice production. There are large existing databases of acoustic signals of speech that should be exploited. Parallel studies of major categories of voice disorders are also needed to determine if sufficiently distinctive profiles make it possible to use this tool for the detection and characterization of specific disorders. Attention to longer-epoch variability in sustained-vowel signals is needed, as well as investigations using protocols containing words and sentences.

Aeromechanical and Respiratory Measures

Laryngeal lesions can disrupt the normal pattern of valving during speech. These lesions affect vocal tone and result in intentional and unintentional alterations in breathing and temporal patterning of continuous speech. There is a lack of aeromechanical data on continuous speech, voice-to-voiceless transitions and altered speech breathing parameters.

Inverse filtering has made it possible to study the alternating current and direct current components of the airflow signal. There is a need for additional information regarding the ultimate usefulness of airflow and air pressure signals in differential diagnosis and for quantifying the effects of various phonatory therapies.

Imaging

There have been technological advances in the imaging of the larynx and pharynx. Magnetic resonance imaging provides near real-time visualization of the vocal tract in reconstructed three dimensions. These images will improve the understanding of laryngeal adjustments and the role of the vocal tract in shaping acoustic signals. Currently, ultrasound has limited application for laryngeal viewing, given the poor resolution of the images. The usefulness of the technology remains to be determined, with the potential application awaiting improvement of image quality.

Imaging of the entire upper aerodigestive tract is currently most often performed with videofluoroscopic techniques. These techniques are undergoing precise quantification that will provide a database for normal and disordered function, particularly for evaluation of dysphagia. Advances in signal acquisition and computer enhancement will likely reduce radiation dosage. Magnetic resonance imaging should eventually provide similar information regarding swallowing. Additional information on swallowing is emerging from scintigraphic investigations of normal and impaired populations. Research should continue in all of these technologies to promote a greater understanding of the complex interactions of the upper aerodigestive tract.

Direct visualization of the laryngopharyngeal region continues to improve with advances in fiberoptic endoscopy. The widespread application of fiberoptic endoscopes has improved patient care and provided the means for direct observation of those sites. Further improvements should be pursued in this technology in the areas of image quality and analysis. Quantification of laryngeal images must be strengthened, and meaningful parameters should be developed for application of these images in research and clinical settings.

Videostroboscopy of the larynx through the use of fiberoptic endoscopes remains the best available technology to acquire laryngeal images in view of the inherent technological limitations of high-speed laryngeal photography. However, both technologies require further use with other measures to help relate structure to dynamic voice production. Recent technical developments using semiconductor sensor arrays promise direct digital storage of endoscopic images to provide sufficiently high frame rates to evaluate aperiodic movement of the vocal folds.

Structural and dynamic imaging of the brain have rapidly advanced to provide new insights in the organic basis of voice and swallowing disorders. Magnetic resonance imaging should be further used to investigate potential structural lesions in the central nervous system in various populations. Functional or dynamic imaging through the use of positron emission tomography and signal photon emission computed tomography should be applied to improve the understanding of control of the upper aerodigestive tract in normal and disordered populations.

Observations obtained by using a combination of these technologies should be related to each other and to measures from nonimaging techniques to develop appropriate models for understanding voice production.

Augmentative and Alternative Voice Sources

Paralysis due to stroke, tumor or infection greatly alters the ability of the larynx to perform its vital functions of airway protection, respiration and phonation.

Advances have been made in the development of electronic, artificial larynges (external, internal and implantable) and in tracheoesophageal shunts (with and without alloplastic voice prostheses). Further study in this area is needed. Also important are efficacy studies to evaluate the relative benefits of these prostheses and to predict which prostheses are appropriate for various populations.

New technologies in signal processing now make it possible to activate individual laryngeal muscles at the precise moment that they are needed for subserving the diverse requirements in speaking, swallowing and breathing. Several laboratories now have the capability to pace electrically the paralyzed vocal fold to reestablish its abduction. Additional studies should enable investigators to evaluate this procedure.

If scientists are to extend electric pacing to a greater complement of individual muscles in the larynx, they must systematically define the best electrode configurations to give consistent and optimal stimulation strategies. Basic knowledge of muscle denervation is limited. Little is known, for example, about the effects of electric stimulation on the preservation of muscle integrity, which is known to degenerate when the muscle is separated from its nerve. In many respects, laryngeal investigation could serve as a model for other medical scientists involved in electric pacing.

Although a variety of communication devices and aids has been developed, individuals utilizing a voice source are limited in the number of voices available and the naturalness of the vocal quality. Research is needed to develop and make accessible an unlimited repertoire of voices to allow each individual the choice of a unique and acceptable voice. Furthermore, dynamic control of vocal quality, if possible, will enhance communication functions greatly. Research should be undertaken to develop instruments with a wider range of frequency, intensity and timing characteristics that will closely mimic natural vocal characteristics. The end result should be access to affordable technology.

One of the major purposes of communication is to express affect or emotion. Control of voice source characteristics, including appropriate aperiodicity and spectral envelope, is vital for these purposes. In the development of augmentative and alternative communication devices and aids, research is needed to develop the paralinguistic features of stress, intonation and juncture that are important in deriving the full meaning of vocal behavior.

Surgical Tools

Recent developments in surgery related to new methodologies such as the intraoperative monitoring of laryngeal kinematics and viscoelasticity have given the surgeon the potential to alter reliably the structure and improve the function of the larynx. Phonosurgery, designed to alter vocal output, focuses on the modification of laryngeal biomechanics to increase or decrease vocal fold stiffness or closure to improve the acoustic source characteristics of the larynx. These operations are undergoing further refinement. As familiarity with existing and new surgical approaches increases, several research areas should be addressed:

- Encourage simulation modeling to predict the effect of modifying the individual elements controlling laryngeal function to tailor specific procedures to specific disorders.
- Compare the efficacy of existing and new procedures using longitudinal outcome studies.
- Conduct intraoperative assessment of vocal function by selecting parameters.
- Conduct intraoperative monitoring to prevent injury to laryngeal structures or nerves during surgery.
- Develop new alloplastic and use autogenous augmentative materials, based on the molecular and cellular structure of the tissues.

Medical and Behavioral Treatment

There is a critical and continuous need for research to develop and evaluate the efficacy of medical, surgical and behavioral treatment for voice disorders. With the rapid evolution of treatment, concern exists regarding the development and standardization of measures for assessing the results. Despite recent advances in knowledge concerning which diagnostic techniques are likely to produce the highest yield for specific disorders, there is limited information on reported measures as they relate to the underlying pathophysiology. There is no clear understanding of how to use these results in making treatment decisions. With the emerging era of quantification of voice production, objective techniques should be applied to assessment of treatment.

In addition, behavioral studies are needed to determine which treatments are effective. Such quantification should enhance decisions as to the timing, selection, contraindications and outcomes of treatment options. Studies of large populations of normal and disordered speakers are needed to clarify the relation between quantitative measures and vocal characteristics accompanying different treatment alterations of laryngeal configuration and behavior.

Computational Analysis, Modeling and Speech Synthesis

Methods of computer simulation of vocal fold vibration have been effectively used to compare physiologic mechanisms and their control to acoustic signal characteristics in speech production. Past contributions have concerned voice fundamental frequency and intensity control. Recent progress has been made in understanding physical principles that determine the acoustic power generated or efficiency of producing voice power as the output for a given input of respiratory power. Additional research is needed. Understanding the mechanical cause of damage to the tissues is an example of the clinical implications of such research.

Voice-quality control is one of the major areas of voice science in the coming years, with important applications in areas ranging from speech development and voice disorders to speech technology such as text-to-speech synthesis and automatic recognition, as well as automatic speaker identification. To address these advanced areas of speech research, it is necessary to use fully emerging, computational tools, both hardware including high-speed digital signal processing boards and software including high-level computer languages and graphics tools. It is also essential to develop more detailed models that relate controlling muscle contractions to vocal fold configuration and properties including nonlinear phenomena. Also critical is the modeling of the surrounding structures related to the larynx as well as pharyngeal gestures, in part in relation to articulatory gestures involving the tongue and the mandible.

To be able to specify voice characteristics from a communicative functional point of view, there need to be effective descriptive systems for representing extralinguistic specifications of utterances including, in particular, emotional elements, as well as linguistic specifications including prosodic information. It is important to understand and specify quantitatively temporal properties such as exact characterization of aperiodicity, as well as spectral characteristics, not only for describing the abnormal voice and idiosyncrasies of speakers, but also for prosodic and affective uses of voice.

As a physical phenomenon, vocal fold vibration has received some new attention in connection with the emerging concept of physical chaos, a deterministic but apparently random process. This point of view has not produced immediately useful results, but it holds promise for understanding the basic nature of voice production and, quite plausibly, may also provide new insights into vocal quality issues.

At the same time, new ideas need to be implemented in more realistic and effective computational modeling of the vocal fold vibration processes, such as the role of surface tension and other tissue surface properties that have been largely neglected. Such new modeling work may be expected to provide not only new understanding, expanding the coverage of phenomena explained, but also evaluation and correction of previous modeling work that was constrained in terms of computational feasibility.

Modeling work is sometimes difficult to evaluate; however detailed the model is intended to be, simplifications, and quite often oversimplifications, are inevitable. One general methodology to use to solve this problem is to synthesize speech signals according to the conclusions about critical elements of control in the given model and to evaluate the signal characteristics by human perception when control is altered factor by factor. Also, by comparing generated signal characteristics with analyzed natural speech signals, a precise, parametric description of observed speech phenomena can be obtained through analysis by synthesis.

Psychophysical and Perceptual Measures

Voice characteristics constitute an important aspect of speech perception. Perception is the ultimate process of evaluating the relevance of voice characteristics to communicative functions, and all findings and hypotheses eventually must be evaluated with respect to their perceptual effects.

Most psychophysical experiments in the past had to deal with either simple phonetic samples (such as consonant-vowel syllable for consonant identification) or subjective labeling of complex stimuli (as in emotional states). Statistical assessment of a large number of comparisons between physically similar and dissimilar samples also provides objective and quantitative decomposition of psychophysical properties.

A new method is emerging to help determine objectively the auditory perceptual properties of voice. Auditory images can be computed by simulation according to specific models and presented visually for another type of subjective judgment. The difference from a listening evaluation of the acoustic signal is that one can point to a particular pattern or characteristic of the displayed image and discuss it. Also, as soon as pattern characteristics are explicitly identified, measures or criteria can be implemented as computational algorithms to have a machine perform the same judgment tasks more rigorously according to given criteria and more extensively, covering a larger amount of data.

There are a number of artificial intelligence techniques, such as expert systems and neuronetworks, that can be useful for such combinations of human evaluation and formal algorithmic procedure. In a sense, this is a new research methodology that can supplement or in some cases replace straightforward statistical inference in data analysis. This methodology can be particularly effective for quantitatively describing and characterizing complex phenomena such as vocal quality in conversational speech. Although statistical data reduction should be encouraged for quantifying research findings, innovative quantitative methods of data interpretation also should be studied.

Measurement of Laryngopharyngeal Gestures

Voice quality is controlled by subtle alterations in the setting or resetting of laryngeal and pharyngeal postures, such as laryngeal height, supraglottic constrictions and agonistic or antagonistic interaction of the intrinsic and extrinsic musculature. Measurement of these gestures can be directly or implicitly obtained with a variety of techniques. These include electromyography, electroglottography, photoglottography, high resolution magnetic resonance imaging, inverse filtering, stroboscopic imaging, direct fibroscopic imaging and digital storage.

Limitations exist in each technique. For example, glottography signals are the sum of vibrations occurring from each vocal fold; thus, in isolation, they seldom are diagnostic. Stroboscopy creates a montage by averaging images over many cycles; its analysis is often subjective and it cannot be used to describe highly chaotic vibration. Inverse filtering relies on assumptions regarding linear, nonturbulent source tract interaction.

Multidimensional simultaneous approaches are advantageous in that the deficiencies of a particular measure may be counterbalanced by the advantages of other techniques.

Areas for investigation include the functional relevance of objective evaluation of kinematic and oscillatory signals or images during normal voicing and under conditions of compensation and adaptation in pathologic states.

Summary of Research Recommendations

Major Basic and Clinical Research Opportunities

Normal Structure and Function

Respiratory, Laryngeal and Upper Aerodigestive Tract Physiology

- Study the nature of respiratory, laryngeal and upper aerodigestive tract actions and interactions in voice production and determine the principles that govern adaptive and maladaptive behaviors in response to laryngeal disorders or diseases.

- Gather data on voice production that encompass various domains, including neural, muscular, structural, aeromechanical, acoustical and perceptual domains.

- Conduct research to delineate further the effects of bolus characteristics, respiratory parameters and voluntary control on timing and extent of laryngeal elevation and closure and pharyngeal contraction during swallowing.

- Conduct studies on the mechanisms involved in the control of vocal pitch, loudness, quality and register, including mechanisms associated with singing.

- Study the role of sensation, including hearing, vibrotactile sensation, proprioception and respiratory cues, in the development and use of voice in normal, impaired and exceptional subjects.

- Delineate the acoustic to perceptual transformation in voice-quality disorders, with special attention to those aspects of the voice signal that give rise to the perception of disorder and its quantities.

- Study the timing mechanisms of laryngeal behavior in coordination with respiratory and articulatory activity.

- Conduct studies on the exceptional (trained) singer to specify the limits of the human voice and its optimal efficiency.

- Determine the effects of lifestyle choices (diet, smoking, drug use, exercise and alcohol consumption) on the function of the larynx and upper aerodigestive tract.

Neural and Vascular Mechanisms

- Conduct studies of neural control of the larynx for voice production, respiration and swallowing in humans and animals, including the elucidation of reflex mechanisms for each.

- Use transcranial magnetic stimulation and sensory evoked potentials to map cortical areas pertinent to laryngeal function.
- Determine the activity of the brain stem motoneuron pool during different phases of respiration, phonation and swallowing via the use of short- and long-latency reflexes elicited through electrical stimulation of the recurrent laryngeal nerves.
- Obtain information concerning the function of neural sensors in the control of voice production.
- Determine the similarities and differences in human laryngeal physiology to that of other species proposed as models for human voice production and swallowing.
- Use electrically or chemically elicited phonation from the periaqueductal gray area of the midbrain in anesthetized animals to study the behavior of laryngeal motoneurons, sensory afferents of the larynx and mechanisms of phonatory control.
- Conduct studies of blood circulation and its autonomic control in laryngeal tissues and the relations to biomechanical changes in the larynx, vocal fatigue and laryngeal lesions.

Biomechanics

- Develop common spatial and relational references for laryngeal function to make it possible to gather multivariate data to enhance the modeling of laryngeal function and dysfunction.
- Determine the importance of lubricating fluids on the vibratory function of the vocal folds and study the composition and aberrations of these fluids.
- Conduct studies of the material properties and biomechanical behaviors of laryngeal structures.
- Determine the physiologic consequences of muscular atrophy of the upper aerodigestive tract on vocalization, swallowing and respiratory function.

Development and Aging

- Conduct studies of the mechanisms of epithelial-mesenchymal tissue interactions that are a driving force in the normal development of the larynx and its final form.
- Specify the nature of voice production as it relates to the developing structure of the entire respiratory system and upper aerodigestive tract and larynx in particular.

- Obtain data on laryngeal and upper aerodigestive function of normal octogenarians, nonagenarian and centenarians for voice production and swallowing.

Cellular and Molecular Biology and Anatomy

- Specify the sites of hormonal influence on the respiratory system and upper aerodigestive tract and larynx in particular, as well as hormonally affected changes in voice production.

- Determine the biochemical and structural specializations characteristic of laryngeal muscle fibers and their innervation.

- Define the distribution of extracellular matrix molecules, oncogene expression, growth factors and growth-factor receptors as they relate to normal structure of the aging larynx.

- Conduct studies of the cellular biology of cartilage and joint deterioration in the larynx as they affect voice production and swallowing in aging.

Diseases and Disorders of the Larynx and Upper Aerodigestive Tract

Epidemiology and Prevention

- Gather data on the incidence and prevalence of voice and swallowing disorders.

- Conduct epidemiological surveys of the influence of external environmental factors on voice production to identify important agents and clarify pathophysiology and develop strategies for prevention, diagnosis and management of the resultant voice disorders.

- Identify genetic and environmental causes of congenital disorders of the larynx and pharynx.

- Develop strategies for prevention and early detection of cancer of the upper aerodigestive tract.

- Conduct epidemiological and case-control studies to identify factors which may lead to focal dystonias of the head and neck.

Pathophysiology and Potential for Improved Therapy

- Improve the understanding of infectious and allergic disorders of the upper aerodigestive tract and develop better therapy.
- Identify and study genetic influences on laryngeal function and dysfunction.
- Obtain information on the effects of drugs (alone or in combination with other therapy) on the voice.
- Study the role of psychogenic factors in the pathogenesis of voice disorders and response to treatment and develop criteria for distinguishing psychogenic from organic voice disorders.
- Determine the role of extracellular matrix, growth factors and oncogenes in wound healing of the larynx and in the pathogenesis of laryngeal and tracheal stenosis.
- Determine reasons for gender differences in susceptibility to vocal disorders.
- Study the effects of aging on voice production to establish the true nature of age-related voice (not pathologic) changes and develop treatment to forestall or prevent such changes.
- Study the effects of respiratory disorders on the voice.
- Conduct studies of recurrent laryngeal nerve regeneration as well as denervated laryngeal muscles to improve the understanding of pathogenesis and treatment of laryngeal paralysis.

Evaluation of Current Therapy

- Conduct prospective, controlled trials to assess effectiveness of treatment for voice disorders, including phonosurgical procedures and voice therapy.
- Conduct long-term, large-scale studies of the management of laryngeal papillomata to address recurrence rates, effects of treatments, effects of cofactors and rates of association with carcinoma of the larynx.
- Evaluate prospectively the effects of conservation surgery for upper aerodigestive tract malignancy on speech, swallowing and breathing.
- Determine the effects of irradiation and chemotherapy on laryngeal function.
- Conduct prospective trials to develop criteria to predict optimal dosage and placement of botulinum toxin injection in the management of focal dystonias and to determine the long-term effects of this therapy.

- Characterize the diffusion of botulinum toxin in tissues and determine whether retrograde transport to the brain stem accounts for some of the substance's therapeutic actions.

- Conduct studies of the effects of acid and alkaline gastroesophageal reflux on voice and swallowing and evaluate the efficacy of treatment for these disorders.

Technology

- Use simulation modeling to predict the effect of modifying individual elements controlling laryngeal function and account for the effects of surface tension, other tissue surface properties and the specific effects of muscle contractions, including nonlinear phenomena.

- Use magnetic resonance imaging and positron emission tomography to seek structural lesions in the central nervous system in patients with voice and swallowing disorders and to improve understanding of the control of the upper aerodigestive tract.

Diagnosis

- Conduct studies on large populations of normal and disordered speakers to clarify the relations between quantitative measures and perceptual vocal characteristics to determine how to use quantitative measures in making treatment decisions.

- Determine the usefulness of aeromechanical measurements in the differential diagnosis and assessment of treatments for vocal disorders and evaluate the contribution of the respiratory system to aerodynamic measures.

- Develop meaningful parameters to evaluate quantitatively laryngeal visual images.

- Study the impact on laryngeal electromyography of variations in electrode configuration, interaction of electrodes with muscles, techniques used to verify electrode placement and testing protocols.

- Develop techniques for nonvoluntary activation of laryngeal nerves as a means of verifying the integrity of laryngeal nerves in uncooperative or anesthetized patients.

Treatment

- Conduct studies of electrical pacing of the larynx to evaluate the procedure and determine its long-term efficacy.

- Develop prosthetic speech instruments which mimic natural voice characteristics and express paralinguistic features of stress, intonation and juncture.

- Develop and determine the usefulness of techniques for intraoperative monitoring and assessment of vocal function in improving surgical results and preventing complications.

SPEECH AND SPEECH DISORDERS

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SPEECH AND SPEECH DISORDERS

Overview

Contributions of Basic and Clinical Research to Understanding Speech

Speech and language are so closely related that many people may regard them as synonymous. But speech is only one of several media through which language can be expressed. Other means of expression include natural manual language systems such as American Sign Language and formal representational systems such as the graphic symbols of the written or Braille alphabets. Speech is remarkable because it is nearly always the primary medium of language expression. For people with sufficient sensory, motor and cognitive capacities, speech is also the first-learned means of expression. Interestingly, the word infant means "without speech," reflecting the commonly held assumption that the most important feature of a baby is its inability to talk. Because speech and language are closely connected, their disorders are not always easily distinguished. Moreover, speech disorders often accompany language and voice disorders.

Speech disorders affect a large number of children and adults. Generally, speech disorders include articulation disorders, prosodic disorders and fluency disorders. They have many causes, including hearing impairment, neural dysfunction and structural anomalies as well as other conditions of unknown or uncertain etiology, referred to as idiopathic. Included in this classification is a large proportion of speech sound (phonological) disorders and stuttering. Although the etiology is unknown, these disorders have been suspected to involve difficulties with the motor control of the muscles associated with speech. Recently, it has been recognized that idiopathic disorders also are associated with impairments in the processing, organization or mental representation of linguistic information.

Speech is produced by precisely coordinated muscle actions in the head, neck, chest and abdomen. During speech development, the child learns how to regulate these muscles to produce intelligible speech. In fact, children learn to produce intelligible speech organized according to the detailed sound patterns of the specific language, indeed, the specific dialect spoken in their homes. How do they learn to reproduce the specific patterns of that language and dialect? At its core, this achievement reflects a remarkable interplay between children's perception of both general and language-specific patterns in the speech input from others and their increasing ability to shape the details of their own speech productions according to that input. The perceptual information that makes this possible is provided predominantly, but not solely, through the auditory sensory modality. Important information also comes from additional modalities, including the visual (speechreading), the haptic (touch) and the proprioceptive modalities (perception of self position and self movement).

A number of studies have shown that adults, children and even infants integrate visual dynamic information about lip movements with the auditory signal when perceiving speech. Infants a few months of age can relate this information to their own corresponding orofacial movements in imitations, suggesting a strong (possibly innate) sensorimotor linkage. The complexity of this developmental interplay between perception and production is underscored by the multiple levels of organization in the sound structure of the native language (consonants and vowels, words, prosodic patterns) and their disruption in developmental speech disorders.

The complexity of the developmental process is indicated by the fact that children's mastery of native language speech sound production is not complete until at least six years of age and perhaps even as late as adolescence. Although speech is a highly robust medium of expression for language and is considered by many experts to be automatized after language acquisition is complete, it is vulnerable to various disturbances that can affect the child or adult. To understand the etiology and nature of these speech disorders, it is essential to recognize the major processes that are involved in speech production and in the perception of speech.

The system of speech production typically is regarded as having three subsystems: respiratory, laryngeal and articulatory. The respiratory system generates the air pressures and flows that provide the basic energy for speech sounds. As the air from the lungs is forced through the larynx (voice box) in the neck, the airstream may be valved in a number of different ways. The airstream may pass rapidly through an opening between the vocal folds; its flow may be momentarily blocked by the vocal folds held in a closed position; or it may interact with the vocal fold tissues, causing them to vibrate and thereby generate the sound of the voice. Above the larynx the articulatory subsystem consists of the pharynx (throat), tongue, lips, jaw, and velum (soft palate). These articulators act to shape the resonating cavities known as the vocal tract. Any mechanical or neurogenic damage to any part of this system can result in a speech disorder.

Hearing is critical to the normal development of speech. As noted earlier, it is the primary source of information for learning about the language-specific patterns which must be mastered for competence with a spoken language. Although it is often said that perception abilities develop in advance of the corresponding production skills, recent findings indicate that perception continues to evolve through childhood and even into adolescence. For example, recent evidence shows developmental changes in infants' categorizations of native and nonnative speech sound patterns. Moreover, the growth of linguistic knowledge in older children causes corollary changes in perception of speech. Children differ from adults in their speed of recognition of words, their reliance on linguistic and cognitive expectancies and their ability to understand speech in noisy conditions.

Improving scientific understanding of these developmental changes is important not only in its own right, but also because at least some difficulties of speech production can be traced in part to difficulties with speech perception. At the extreme, children who are born with a severe hearing impairment, or who acquire such an impairment before they learn spoken language, are at high risk for difficulties in speech and language acquisition. Even adults, who acquired language normally as children, may experience a slow deterioration of speech if they acquire a hearing impairment. Speech perception deficits resulting from less serious hearing impairments, or from other speech-processing difficulties, may be associated with language-related difficulties, including poor reading skills.

When children enter the first grade, ten percent are estimated to have moderate to severe speech disorders, such as missing sounds, substituted sounds, or stuttering. The speech of some of these children is virtually unintelligible to people outside of the child's own family circle. Most of these disorders are idiopathic. Legislation now requires that states provide early intervention for these children to assist them in developing speech. Approximately 80 percent of children with such speech disorders require special education services, and 50 to 75 percent of them evidence other, more general, academic difficulties. The majority of these children who have speech-impairments do learn normal speech, but about 20 percent will have lifelong speech disorders. And even among those whose speech impairments are no longer obvious to listeners, adults who had phonological disorders as children often continue to have general difficulty with phonological information, for example, impairments in reading and spelling ability. Such persistent difficulties limit the affected individuals' educational, professional and social opportunities.

Speech disorders may accompany mental retardation, emotional or psychiatric disorders and a number of developmental disabilities. In addition, over 30 million Americans (12 percent of the United States population) speak a language other than English as their first or primary language. Of these, over six million are nonproficient with English or do not speak English at all, according to recent census statistics. These non-native and nonstandard English speakers may have difficulties or differences in perceiving and producing the sound patterns of mainstream English. Although these difficulties do not constitute speech disorders per se, they may have a significant negative impact on academic, vocational and social opportunities. Difficulties with or differences from the speech of the majority language and dialect may present obstacles to these individuals and to their employers, employees, students and offspring.

Speech disorders and poor command of English can greatly hinder academic achievement, vocational success and social adjustment. Disorders and other limitations on speech production and perception affect not only ordinary social communication but also efforts to use telecommunication systems. Recent progress in the design of voice-controlled computer systems is evidence that technological advances may further increase the importance of speech communication for participation in a technological society. Individuals with limitations of speech communication can face several risks or disadvantages, including poor academic performance, higher likelihood of school dropout, limited employability and reduced opportunities to engage in continuing education or training to keep pace with a changing job market.

Disorders of Speech

The importance of basic research in the understanding of speech was brought out in the preceding section. Subsequent information will include disorders of speech and the consequences of disordered speech. To appreciate the importance of improving the scientific understanding of speech, its development and breakdown, brief summaries of the primary, recognized speech disorders are helpful.

Structurally Based Disorders

Many individuals with congenital anomalies of the speech production system (cleft lip and palate or multiple anomaly syndromes) or acquired structural defects (a result of cancer surgery) may have moderate to severe difficulties in producing speech sounds, whereas others are apt to produce intelligible speech. Clefting of the lip, palate or both occurs in about 1.2 of 1,000 births. Children born with congenital craniofacial anomalies are vulnerable to deficits in virtually all areas of communication development: cognition, hearing, perception, language, voice, articulation and phonology. In these children, sensitive periods for development of communication skills are affected by the presence of structural defects, by the surgical procedures to correct the defects and by adverse interpersonal factors both in and outside the family. Individuals with acquired defects may be affected by many of the same factors.

Neurogenic Disorders of Speech and Swallowing

Motor speech disorders, the dysarthrias, can occur in almost all diseases of the central nervous system. Figures from the National Foundation for Brain Research (1992) suggest that about one million individuals in the United States experience a neurogenic impairment of speech. That translates into a prevalence of about 4 per 1,000 individuals. Reduced speed and accuracy of movement of the pharynx, tongue, lips, velum and vocal folds impair speech of people with Parkinson's disease, amyotrophic lateral sclerosis, Huntington's disease, multiple sclerosis and other diseases. Injury to the brain centers involved in speech production and control affects the programming and sequencing of sounds in speech dyspraxia. Motor speech disorders are common because any disturbance in movement control will affect the accuracy and speed of articulatory movements and because complex coordination of the respiratory, phonatory and articulatory systems is needed to produce speech.

For some individuals, motor impairment of speech is so severe that natural speech is not an effective means of communication. Historically, many of these individuals have used alphabet or word boards to communicate. Others have relied on simple gestural systems, such as responses to yes and no questions. The advent of portable electronic aids has markedly expanded the communication options for individuals with severe disabilities.

Oral motor dysfunction that interferes with the production of understandable and natural sounding speech may also impair swallowing. However, swallowing is sometimes impaired when speech is not. Major swallowing disorders, the dysphagias, accompany many injuries or diseases affecting the central nervous system. Because adequate oral movements are needed for safe and effective swallowing, individuals with swallowing impairment may not only have difficulty in meeting calorie and fluid intake needs but also may be at risk for aspiration and its profound consequences. In 1989, it was estimated that there were 6 to 10 million people with swallowing disorders. Neurogenic impairments account for about 80 percent of the cases of oropharyngeal dysphagia. Stroke, in particular, frequently results in swallowing problems, with as many as 25 to 50 percent of stroke patients having some difficulty in swallowing.

Stuttering

Stuttering is most often manifested by repetition and prolongation of sounds and syllables, usually in the initial portion of the word. Although individuals who stutter appear to know what they want to say, their ability to initiate and maintain the motor aspects of speech production often becomes disrupted. Different studies estimate the prevalence of stuttering in school-age children to be between 0.5 to 2.2 percent of the total population; on average, approximately one percent of school-age children stutter. The number of adults who continue as chronic stutterers is less certain, but the prevalence of stuttering in adults is probably less than one percent. The problem can have serious academic, emotional, social and vocational consequences. Current theory as well as clinical and experimental information converge on the notion that stuttering arises from a complex interaction among variables including genetic predisposition, psychosocial, physiological, speech and language development. There is considerable individual variation in the number and nature of risk factors for the problem of stuttering just as for many other speech problems.

Articulation and Phonological Disorders

A majority of speech disorders are idiopathic (no known cause). These functional speech disorders affect primarily the phonology or sound system of a speaker's language. Although they have been viewed as a possible motor dysfunction, namely, a difficulty in the motor control of articulators and the coordinated, connected production of speech sounds, it has become apparent that they can also involve the general processing, organization and mental representation of linguistic information. Phonological disorders affect an estimated 10 percent of children in the first grade. Children with functional speech disorders constitute approximately 90 percent of the students requiring the attention of clinicians working in the schools. These problems can have consequences throughout the lifespan, broadly affecting the individual's educational, vocational and social opportunities.

Speech of Persons Who are Hearing Impaired

The role of auditory feedback in speech production is complex and changes over the lifespan of an individual. Based on household interviews in the 1990-91 Hearing Supplement to the Health Interview Survey of the National Center for Health Statistics, approximately nine percent of Americans were estimated to have impaired hearing. Among these individuals 5.5 percent (1.1 million) were estimated to have experienced hearing loss before age three.

Hearing impairments during the early formative stages of speech and language result in a wide variety of speech disorders, reflecting the degree of hearing impairment, the age of onset of impairment and the duration of impairment. Several common patterns of errors are found in the speech of young children with profound hearing impairment, including inaccurate sound production and inappropriate manipulations of prosodic features (pitch, loudness and duration).

Various types of assistive listening devices are currently used to maximize sensory feedback to children and adults with profound hearing impairments.

These devices include alternative sensory information provided by means of taction, amplification or signal processing of stimuli delivered by hearing aids and electrical stimulation of intact auditory nerve fibers via cochlear implants. Adults who lose hearing after developing normal speech experience deterioration in speech production; however, the amount of deterioration they experience appears related to age at onset, the duration and amount of hearing loss. Restoration of limited hearing through the use of cochlear implants indicates that adult speakers often use information from the implants to adjust respiration, phonation, articulation and resonance to more nearly approximate functioning in normal hearing speakers.

Augmentative and Assistive Systems

Augmentative and assistive systems are used by individuals who are temporarily or permanently unable to speak. These people have a variety of disorders, including cerebral palsy, spinal cord injury, traumatic brain insults, motor neuron disease, mental retardation, sensory impairments, affective or psychiatric disorders and acquired cognitive or language impairments. Rapid technological advances have greatly improved the capability of these systems to meet the communicative needs of their users. Systems can be tailored to many individual requirements and some progress has been made in understanding how the use of various devices facilitate communication in children and adults.

Speech Perception Impairments

The fact that hearing impairments adversely affect speech production underlines the central role of auditory input for perceiving how to produce the sounds of speech. Although information from other modalities, such as the visual system, also contributes to speech perception, it generally provides insufficient support in the absence of audition to guide the development of normal speech unless it is augmented. Speech perception is adversely affected to varying degrees and in different ways by impairment of either the peripheral part of the auditory system (ear, cochlea, auditory nerve) or the central part of the auditory system (pathways and neural centers of the brain). Deficits in the ability to perceive speech sounds accurately may interfere with an individual's ability to comprehend spoken language and engage in effective oral communication. Some children and adults with phonological and articulatory disorders may be deficient in speech perception even in the absence of frank auditory system impairments. Phonological or articulatory disorders may also be associated with other defects in linguistic and cognitive functions, such as reading disabilities, childhood developmental language impairment and decline in cognitive function.

Multicultural Issues

The incidence and impact of speech disorders on individuals may vary substantially among different ethnic groups and subcultures. Demographic trends reported by the United States Bureau of the Census indicate that the proportion of minority individuals in the United States is increasing. For instance, the African American population has increased from 26.5 million in 1980 to nearly 30 million in 1990. That represents a growth rate of 13.2 percent, which is one-third higher than the national growth rate. The number of Hispanic Americans has increased by 53 percent, from 14.6 million to 22.4 million, during that same time period. The Native American population has also rapidly increased by 38 percent from 1.4 million to nearly 2 million. The number of Asian/Pacific Islander Americans more than doubled from 3.5 million in 1980 to 7.3 million in 1990.

Given the changing demographics of the United States population, it has been projected that by the middle of the twenty-first century the majority of the country's citizens will be members of minority groups. The importance of diversity within the United States population is all the more compelling when one considers that the major ethnic groups are not homogeneous but consist of individuals and subgroups with varied communication patterns, health risk factors and cultural experiences.

Recent Accomplishments

Speech Production and its Disorders

Speech Production Across the Lifespan

In the past ten years, remarkable advances have been made in the study of speech production. No single experiment or methodology predominates achievement in this decade. Rather, substantial progress in many different areas made the decade a period of broad advances in the study of speech production.

Many significant advances in the past decade have been technological in nature. Through improvements in biomedical instrumentation, it is now possible to transduce a large variety of physiological signals generated by respiratory, laryngeal and orofacial systems, such as movements of the lips, jaw, tongue, velum, vocal folds and chest wall; air flows and volumes; and muscle activity from all of the speech subsystems. Not only is it now possible to measure many different physiological signals, but in many cases the instrumentation is commercially available, so that many different laboratories use the same or very similar instruments. In addition to the improved capabilities for the transduction of signals, advances in widely available personal computer systems have revolutionized techniques for the digitization, storage and subsequent analysis of speech-related signals. It is possible to collect simultaneously many different types of data, including recordings of the electrical activity of muscles (electromyography), structural movements, air flow and acoustic waveforms over relatively long samples of speech. Investigators are now able to devise creative approaches to long-standing problems because commercially available software packages make it relatively simple to implement digital signal processing techniques for the analysis of speech-related signals.

These technological advances represent a revolutionary change in speech production research. First, the sound generated by a talker is a product of coordinated, multilevel motor processes involving the lower respiratory tract, the larynx and the supralaryngeal vocal tract. Given the many levels of activity in the control of vocal tract changes needed to form speech, their complexity and the potential for interactions between systems, an understanding of speech production rests on an understanding of all components involved. The new technology and its wide availability enable different laboratories to take a comprehensive, cross-systems approach to the study of speech production. Until recently laboratories often studied only one articulator, one subsystem, or one type of measurement. For example, one investigator might study only respiratory movements in speech, while another might study only articulatory movements. Such isolated efforts yielded limited insight into the coordination between the respiratory system and the orofacial structures essential for speech production. The new technology has created the potential for standardizing the quantitative analysis of physiological and acoustic signals in large numbers of subjects across laboratories. In the past, studies with small numbers of subjects, often fewer than five, left unresolved issues about the range of individual variation and often failed to delineate common underlying patterns of organization. In summary, the time has passed when digital signal processing of speech acoustic and physiological signals was an esoteric enterprise undertaken by just a few scientists. Speech science has now entered an era in which biomedical technology and computer-based systems have become standard tools for scientists and clinicians interested in the production of speech.

The past decade also has been a time of growth in the theoretical bases for understanding the processes involved in speech production. A significant aspect of this growth is that it has come about through the integration into speech production theory of theoretical and conceptual developments in a variety of other disciplines. For example, many investigators have adopted models from the general motor control literature, and a major goal of research in recent years has been to apply concepts developed in the study of the neurophysiological bases of movement production to the problem of motor control in speech. This point of view has motivated investigations of reflexes, comparative studies of speech and other motor behaviors, such as mastication, and experiments which monitor kinematic and electromyographic responses to transient mechanical perturbations delivered during speech production.

Other theoretical approaches to speech production have incorporated new concepts from the area of nonlinear dynamics developed in fields such as mathematics and physics. Investigators working in this area suggest that speech production is accomplished through the organization of functional synergies or "coordinative structures" that are modeled as coupled oscillatory processes. In addition, the literature on computational models has led to theories of speech production that use connectionist approaches to account for the integration of many different linguistic processes as an input to the speech production system. Connectionist models are a promising means of integrating multiple sources or types of information which may be changing over time such as neural networks. Many new attempts at modeling speech production emphasize the importance of the control of the vocal tract as a whole. One such theory has the idea that articulation emerges from the interweaving of basic gestures into "gestural constellations." A particular attraction of this theory is that it attempts to unify phonological representation with the control of an articulatory synthesizer and acoustic output. This work is important because it models a significant portion of the overall process of speech production.

In summary, it is clear that the theoretical bases for the study of speech production have been expanded and enriched in recent years. General advances in speech production technology and theory have been translated into empirical gains. Experimentation has progressed in a wide variety of areas and includes studies of human subjects (adults and children) and experimental animals.

An understanding of speech production requires a detailed description of movements and muscle activity. Accordingly, many studies in recent years have recorded muscle activity and movement during speech production in normal adult subjects. Such studies have shown that a single speaker frequently uses very different combinations of lip, jaw, tongue, velar and laryngeal muscles to produce the same speech sound on different occasions. Furthermore, there are appreciable differences among speakers. Variation within and among speakers in movement patterns and muscle activity that aims to achieve a common goal is a hallmark of motor systems in general and is often referred to as motor equivalence. Despite these variations in movement patterns and muscle activity in speech, listeners can identify the common underlying phonologic category, an ability referred to as perceptual equivalence.

Although there is variability in physiologic events associated with speech, investigators have proposed that there are some relatively invariant aspects of speech production. For example, a recent study using cross-correlational analyses of recordings of jaw muscle activity demonstrated that consistent muscle synergies are used by various speakers for different tasks. According to the study, speech is characterized by coactivation of antagonistic muscles of the jaw, where other tasks, such as chewing, involve a reciprocal pattern of muscle activation. Another approach to the search for relatively invariant aspects of speech production relies on the analysis of velocity profiles computed from the movement patterns of speech articulators. A consistent velocity profile that retains its major features even though the speaker may change the rate of production or emphatic stress has been interpreted as evidence that a single underlying neural process produces the various movement outputs. Other investigators have provided careful analyses of the sequencing of kinematic events, such as the sequencing of the peak velocity of movement of the upper lip, lower lip and jaw. Some of these studies have indicated that, while the amplitude of movement and muscle activity varies greatly across repetitions of an utterance, the relative sequencing of movement events is quite stable.

Substantial progress also has been made in elucidating the structure of the vocal tract, including hard and soft tissues, with magnetic resonance imaging. Recent advances in this technique should make it possible to undertake population-based studies of the gross structure of the upper vocal tract. New information on articulatory dynamics has been gathered with the X-ray microbeam and vocal tract magnetometry, which permit the simultaneous recording of movements for several vocal tract structures.

Although advances have been made in the last decade to understanding the biochemical and mechanical properties of the muscles of the larynx and mandible, little progress has been made in studies of the tongue and facial muscles. Such studies are particularly important because the muscles innervated by the cranial nerves appear to have unique properties not seen in other striated muscles, such as limb muscles. These studies are also critical in understanding the basic characteristics of contraction and control of the muscles of the face and oral cavity.

Investigations of the peripheral tissues of speech structures are showing the kinds of sensory receptors involved in transducing motor output during speech. Many of these structures may have unusual receptors or lack receptors found in the limb motor systems. For example, the muscle-spindle receptor is found in most skeletal muscles and plays an extremely important role in signaling ongoing movement events to the brain. Many muscles of the human orofacial system have been thought not to contain muscle-spindle receptors. In a recent study, however, new staining and microscopic scanning techniques were used to examine muscles of the soft palate. This technique documented the presence of muscle-spindle receptors in these tissues. This discovery revised ideas about the kind of information the brain receives regarding the movements of the soft palate.

There have been a limited number of studies on the structure and biochemistry of the brain stem, which contains the groups of neurons that innervate the orofacial and laryngeal musculature. A better understanding of these areas of the brain is critical to interpretations of data on normal speech movement production and to understanding various diseases (amyotrophic lateral sclerosis) that produce deficits in orofacial muscle function.

In recent years considerable attention has been given to sensorimotor interactions in the orofacial systems. Studies of reflexes of the oral motor system have revealed that changes occur in these reflexes throughout the lifespan. In particular, it has been found that reflexes operating on the muscles of the jaw, rather than being reduced as the infant grows into childhood, actually increase in amplitude during the period between four to eight years of age. In the elderly, compared to young adults, reflex responses are reduced in amplitude and increased in latency.

In other experiments oral structures have been stimulated during performance of speech tasks. For example, mechanical loads have been applied to the lower lip. These studies have led to the conclusion that even rapid speech movements are subject to sensory correction. The neural pathways involved in producing the plans for the execution of speech movements and in adjusting these plans on the basis of incoming sensory information are largely unknown and are difficult to study in humans. Some recent investigations of the input and output relationships in the primary face area of the sensorimotor cortex of monkeys provided useful data for speculating about the function of this part of the brain in human speech. Investigators stimulated the precentral (motor) area of the cortex associated with the face with very small electrical currents. They observed orofacial muscle responses primarily on the contralateral side; however, responses on the stimulated side were also common. This finding suggests that the face area of the brain may have a more bilateral representation compared to that of the limb areas, at least in nonhuman primates. In addition to stimulating these areas, the investigators recorded the activity of neurons while sensory stimuli were applied to orofacial sites. Most of the neurons in the primary face area of the motor cortex responded to light stimuli applied to the area in and around the mouth. Further, neurons in the primary face area are active during the control of voluntary tasks performed by the monkeys (for example, producing a steady force with the tongue). Additionally, cooling of the brain's primary face area, which temporarily interferes with normal neuronal function, has deleterious effects on performance of the tasks.

Perhaps the most compelling result of these studies of sensorimotor organization of the monkey cortex is the high degree of overlap in representations of the face, jaw and tongue in the primary face area. The intermingled, multiple representation of the muscles of the jaw, lips and tongue suggests an organization that would provide an excellent neural substrate for the generation of coordinated, simultaneous movements of vocal tract structures. Although monkeys do not produce speech, studies of their nervous system can yield important hypotheses about the neural regulation of speech in humans.

In the past decade, there has been interest in extending observations of speech production processes across the lifespan. Important advances have been made in describing infant vocalizations and relating them to their limited movement control possibilities. Detailed taxonomies have been created of vocalization types. The expected sequence of development in the period leading up to the production of the first words has been described for normally developing infants. The data for normal infants are now sufficient to provide a standard of comparison against which to judge the development of infants at risk for speech difficulties, infants with disorders such as Down syndrome or congenital deafness and infants being reared in special environments, such as, bilingual homes. Development of new theory has afforded a means by which to understand how, within a motor system enjoying fewer degrees of freedom, the infant organizes the open-close or close-open movement sequences that adults hear as syllables.

For the first time, research has provided convincing evidence that, prior to production of his or her first words, the infant has begun reproducing sound characteristics of the ambient language. Also, it has become clear that the movement control patterns and gesture types available in producing the sounds and syllables of the babbling "repertoire" are recruited to produce the first words. At around the age of 18 months, the child's vocabulary undergoes explosive growth, with a resultant serious mismatch between the kinds of words the child would like to say and the kinds of words children are capable of articulating. Work in the area of child phonological development has shown steady progress, going well beyond early studies that simply characterized the expected age of mastery of various sounds in the inventory of the native language being acquired. New work has provided insight into patterns by which types of sounds are added to the phonetic inventory. In addition, current work is providing excellent descriptive data on the constraints on sound sequences that are typically observed in the speech of normally developing children.

Phonological processes, which often but not always operate to simplify productive output, have also been cataloged.

For the first time, a sufficiently rich database on child phonological acquisition is available to pinpoint particular processes that are "idiosyncratic," or at least highly unusual. Based on this knowledge, clinicians can characterize as "disordered" many patterns of speech that diverge sufficiently from age-appropriate norms. Comparable work is just beginning in languages other than English. Given that languages exploit different contrastive sound units and sound combination possibilities, a cross-linguistic perspective affords a unique opportunity for determining which phonological processes observed in child speech arise from "universal" factors (that is, derive from immature musculature or motor control) and which represent a genuine deficiency in phonological knowledge or learning.

At the other end of the lifespan, studies of elderly speakers have also documented various changes in the structural and functional properties of speech production. This information is important for a variety of reasons, but particularly because of the need to distinguish normal age-related changes in speech from changes that are associated with disease. Normative data on acoustic and physiologic measures of speech in the elderly are being accumulated, and this information prepares the way for sensitive and efficient clinical assessment.

Disorders of Speech Production

Structurally Based Disorders

In the past decade, two major technological advances have had an impact on assessment and treatment of individuals with structurally based disorders. One is imaging of the vocal tract with magnetic resonance and improved endoscopic equipment; the other consists of surgical and prosthetic approaches to reconstruction. There has been rapid expansion of genetic and dysmorphologic studies, including gene mapping, that provide better understanding of the etiologic heterogeneity of congenital anomalies. Research has also led to greater recognition of the risk of sensorineural hearing loss in clinical entities previously thought to include only conductive loss (such as malformation of the middle ear). There have been improvements in prenatal detection, allowing families to prepare for the birth of a child with a congenital disability. Studies of speech timing (coordination of respiratory, laryngeal and articulatory events) have offered great potential but as yet unrealized impact on treatment recommendations.

There has also been continuing progress in the study of the comparative effects of "early" versus "late" palatal surgery on subsequent speech development of the child with cleft palate. Additional work has contributed to a growing body of knowledge regarding phonetic and phonologic development in the early years of life, before and after palatal surgery. Furthermore, there have been important refinements of technique that can be used for biofeedback in speech therapy, such as, photodetection, electropalatography, accelerometry, magnetometry and nasometry, as well as continued expansion of the anthropometric database for normal and abnormal craniofacial structure. Finally, research has led to an increased awareness of social and family factors that affect communicative interactions of individuals with craniofacial anomalies, extending from study of mother-infant dyads to studies of self-concept and communicative intent in children and adults.

Neurogenic Disorders of Speech and Oral Motor Function

Motor Speech Disorders. Important advances have been made in the ability to quantify speech performance. At present, different laboratories and research centers produce a variety of measures of speech production and muscle system function for individuals with neurogenic impairments. There is growing appreciation that the pattern of speech impairment may differ as a function of disease and may further differ among individuals within a single disease type, as amyotrophic lateral sclerosis.

Neurogenic Swallowing Disorders. Considerable research attention has recently been devoted to acquiring knowledge about the motor control system for both the reflex and volitional components of swallowing. Improved measurement techniques for analyzing neurogenic swallowing disorders and the recent advances in brain imaging have led to an important new understanding of the swallowing mechanism. Studies have also examined muscle actions during swallowing and how they affect various structural and neurogenic disorders. In addition, studies have begun on the impact of a number of intervention techniques to compensate for various swallowing disorders.

Stuttering

Earlier attempts to understand speaking difficulties in stuttering often concentrated on a single speech production structure, such as, the larynx. Although these studies provided valuable and detailed descriptions of speech production behavior associated with stuttering, it is now apparent that motor disruptions in stuttering are not contained in a single structure. Rather, the disruptions are manifest throughout the systems used to produce speech. For example, the excessive tremor or rhythmic muscle contractions characteristic of many instances of stuttering have been found to be correlated across orofacial (articulatory) and laryngeal (phonatory) muscle activities.

Advances have also been made in studying the genetic bases of stuttering. Behavioral geneticists have shown that speech and language disorders tend to run in families; stuttering is very apt to occur in the families of chronic adult stutterers. This finding suggests a genetic predisposition for stuttering in some families. However, it is also apparent that the complex interaction between inherited and environmental factors must be taken into consideration through appropriate genetic as well as statistical modeling to clarify the extent to which heredity may predispose individuals to stutter.

Important advances have been made in four lines of research related to children who stutter: associated communication problems, bidirectional (speaker-listener) influences, normative data pertaining to the onset and development of speech dysfluency and nonspeech behavior associated with early stuttering. With respect to associated communication problems, recent research makes clear that processes including expressive language and speech sound development are associated with childhood stuttering. For example, several studies demonstrated that, on average, 30 to 40 percent of children who stutter also exhibit disordered speech sound articulation. With respect to bidirectional influences, it is known that changes in the conversational partner's speaking rate influence the stutterer's speech, but the details of these rate effects are not fully understood. With respect to the onset and development of stuttering, recent research makes it clear that childhood stuttering can begin suddenly and quickly become quite serious, whereas earlier opinion was that the disorder always had a gradual onset and development. With respect to nonspeech behavior, recent research shows that at or very close to the onset of stuttering, young children who stutter exhibit nonspeech behavior with their faces and upper bodies when they stutter that is different from that exhibited by their nonstuttering peers. Previously, it was thought that such behaviors occurred much later in the individual's development. Thus, the frequency, nature and behavior associated with the dysfluencies of children who stutter, at or near the onset of the disorder, are different from those of nonstuttering peers. This finding support the growing trend to intervene with such children as early as possible, often while the child is still a preschooler.

Research has shown that during their perceptually fluent speech, stutterers exhibit subtle aberrations, for example, slight slowness of and temporal asynchronies in speech production. This finding suggests that at least some stutterers operate, more or less continuously, with a subtly faulty speech production system and that speech dysfluencies, such as sound and syllable repetitions, are the perceptible evidence of breakdown in this system.

Recent research has also shown that adult stutterers show no deficit on simple manual timing tasks (such as tapping a beat) and force control tasks (such as holding a steady force with the finger). However, when complex sequences of finger movements are required, stutterers do not do as well as their nonstuttering controls. Thus, stuttering may not be related to a generalized motor deficit, but may be reflected only in nonspeech tasks that share motor processes (complex temporal sequencing) used by the speech motor production system.

Stutterers' anxiety and fear about speech and speaking situations has long been thought to play a role in either precipitating or exacerbating stuttering, particularly in adults who stutter. Research has recently examined the possibility that stutterers exhibit excessively high levels of autonomic activity, that is, activity in that part of the nervous system activated during many emotional states such as fear, anxiety and anger. When compared with their nonstuttering peers, adult stutterers do not significantly differ in levels of autonomic arousal. However, for all talkers, the act of speaking is associated with high levels of autonomic arousal. This finding suggests that, if autonomic arousal does contribute to stuttering, it does so because the stutterer's motor system is vulnerable to normal levels of arousal, given their already marginal abilities to initiate and maintain speech production with the required speed, precision and sequential control.

Articulation and Phonological Disorders

Functional speech disorders affect primarily the phonology or sound system of a speaker's language. Traditionally, they have been viewed as a possible motor dysfunction, namely, a difficulty in the motor control of articulators and the coordinated, connected production of speech sounds. More recently, this category of disorders has been extended to include the general processing, organization and mental representation of linguistic information. Functional disorders thus may affect a speaker's motor, linguistic or cognitive processing of the speech sounds of the target language. The causes of the disorder are presently unknown, but links have been traced to genetic factors, hearing and learning abilities.

The building blocks, or units of organization, of phonological systems have been a major concern to investigators working from articulatory, acoustic and linguistic perspectives. The goal of these distinct but complementary studies is to identify the relevant categories of normal and disordered productive phonological systems and to determine how these categories emerge and change over time.

Research on functional disorders has focused primarily on the consonant productions of children. Research efforts have included both large-scale investigations tracing the emergence of sound inventories and common error patterns, and studies of individual differences in children's abilities to learn sounds. In general, universal patterns have emerged in the face of wide variation in both normally developing and disordered sound systems. The emphasis of research has shifted from an examination of expected developmental periods and sequences to the identification of the critical components of and breakdowns in phonological organization.

Although the characterization of functional speech disorders has been limited mainly to the consonantal repertoire, there are a number of other phonological components that may be disrupted. Studies of speech intelligibility provide clear evidence that functional speech disorders extend beyond consonant segments. Consequently, it is important to study in children both with and without phonological disorders the development of vowels, suprasegmental aspects of speech such as rhythm and stress and morphologic adjustments (such as the sound changes in related words like electric and electricity). This line of research is especially relevant and timely in light of recent theoretical advances in the field of linguistics that support the organization and mental representation of phonologic information in a nonlinear way. The results of such investigations will also add to understanding of the relevant factors that contribute to intelligible speech. The results will have further implications for understanding speech perception, for developing speech recognition devices and for improving the quality of synthetic speech, especially that used in augmentative and assistive devices for individuals who are severely speech impaired. Additionally, there is often a concurrence among speech disorders, with phonological problems commonly associated with problems of voice, expressive language or hearing. The relationship and precedence among these disorders are not well understood. The degree to which speech disorders occur and interact with other neural and genetic deficits, such as mental retardation, is also not well understood. Finally, current findings on the contribution of speech perception in phonological disorders are mixed, but it does appear that a proportion of these children with speech disorders may also have perceptual deficits that interfere with mastery of the sound system.

The assessment and treatment of functional speech disorders are promising and active areas of research. Acoustic-phonetic evaluation of children's speech has been shown to provide predictors of subsequent learning. Children's production of subtle acoustic distinctions among sounds may be indicative of emerging phonological contrasts that have not yet been mastered. Consequently, these contrasts may not need to be treated clinically. This new finding provides an exciting direction for assessment.

With regard to treatment of phonological disorders, a number of important findings have emerged. Converging research from a number of laboratories has suggested that treatment should concentrate more on the liguistically and perhaps motorically complex aspects of the sound system to facilitate rapid and widespread improvements in children's phonological systems. In other words, teaching children superordinate phonological skills (those typically developing later) seems to aid in their learning subordinate skills (those typically developing earlier).

These treatments depart from long standing clinical philosophies based on the normal developmental progression and need to be evaluated empirically in more detail.

Assessment and treatment of phonological disorders have also benefited from advances in computer technology. Current technology permits a relatively easy coding and analysis of children's sound systems which facilitates the speed and accuracy of the assessment process and improves the clinician's ability to monitor progress.

Individuals learning English as a second language pose a particular challenge to the accurate characterization and assessment of sound systems and the effective treatment of disorders and differences. Limited data are available on how phonological systems develop in languages other than English. Consequently, it is difficult to distinguish problems in learning a second-language phonology from a phonological disorder per se. That makes it extremely difficult to determine clinically whether nonnative speakers of English are exhibiting a disorder or if their divergent sound systems simply reflect differences between the native language and the other languages being learned.

Speech of Persons Who are Hearing Impaired

Restoration of limited hearing by cochlear implants in profoundly hearing-impaired adults and children has been the catalyst for several studies investigating the role of auditory feedback in speech production. Investigators are able to examine speech production with and without auditory feedback by experimentally manipulating information provided by the implants. Studies of adult users contrasting speech produced with a cochlear implant turned on (providing feedback) and off (eliminating feedback) reveal relatively rapid changes in some speech parameters. Alterations in physiological and acoustic indices of speech production are observed in longitudinal studies that track users of cochlear implants. Deterioration of some speech features is noted in individuals who cease using cochlear implants for auditory feedback. The amount and type of information provided by the speech processing strategies of implant users also appear to influence the production of several speech parameters. Information from these studies continues to expand the knowledge base regarding the role of auditory feedback in the refinement and maintenance of speech movements in adult speakers with hearing impairments.

Speech development in profoundly hearing-impaired children also appears to be influenced by feedback provided by cochlear implants, hearing aids and assistive devices through alternative modalities, such as taction. Longitudinal studies reveal substantial increases in the accuracy of speech features with increased experience with a cochlear implant. Speech features also appear to improve with increased use of tactile aids. Improvement in accuracy of some features also occurs for hearing aid users, although the changes are less dramatic. Some studies demonstrated reduced hypernasality and improved accuracy of sound production as the result of training programs specifically designed to be used with cochlear implants or tactile aids.

Interest in the speech changes associated with cochlear implants has stimulated a series of studies designed to improve the measurement techniques suitable for studying the speech of hearing-impaired persons. New transcription systems are being developed that characterize the behaviors of hearing-impaired children which have not been captured by traditional analysis. Acoustic matrices are being tested to provide ways to measure speech improvement that may not be detectable by simply listening to speech. Studies of speech intelligibility are examining the multiple factors contributing to poor speech. Thus, investigations evaluating the role of assistive listening devices in hearing-impaired speech are producing a vast array of tools useful for objectively measuring speech production in all hearing-impaired individuals.

Augmentative and Assistive Systems

Assistance is now available for the most severely speech-impaired persons, those for whom natural speech is nonfunctional because of cerebral palsy, traumatic head injury, laryngectomy, or neurodegenerative diseases such as amyotrophic lateral sclerosis. Talking machines, based on microprocessors or computers, are being used by such individuals to produce speech phrases with only a key stroke. Other specialized systems allow for computer use, thus providing access to writing and other avenues of academic and vocational pursuit. In the past, individuals using augmentative communication devices had permanent impairment as the result of either congenital or acquired disorders. Recently, augmentative communication techniques have also been used to serve the needs of individuals who are temporarily without functional speech. These individuals are typically in intensive or acute care medical settings and may require ventilator support.

Dozens of new devices have become available, allowing previously nonspeaking individuals to signal basic needs, converse, use the telephone and answer in the classroom or other setting. As more augmentative communication systems become available, the task of selecting devices most responsive to the person's needs becomes increasingly challenging. Issues of training to ensure optimum use will be paramount as the devices become more complex.

A number of accomplishments are apparent in recent literature. The first of these is a trend toward examination of the learning requirement of specific augmentative approaches. For example, the ability of literate adults to recall messages encoded with various techniques has been examined. A second research trend is the study of augmentative systems from the perspective of the communication partner. These studies include an examination of the naturalness and acceptability of various components of augmentative communication systems. Finally, a number of studies have examined the use of various augmentative communication techniques in natural settings. These studies have increased our understanding of the vocabulary usage pattern and communicative styles of individuals who use assistive technology.

Speech Perception

The process of speech perception complements that of speech production. Speech perception can be measured through quantitative means, and it can be represented in ways useful for feedback to the listener for shaping his or her own speech patterns. Approaches to studying speech perception differ from those used for studying speech production, largely because percepts cannot be directly observed. Scientific measures of perception must instead rely on indirect evidence, such as adult listeners' verbal or written reports of what they heard when presented with a speech signal. In the case of nonverbal subjects, including infants and animals, researchers must infer perceptual processes from the way in which the subject's conditioned (trained) behaviors, such as head turns or lever-presses, change in response to variations in the speech stimuli presented. Certain physiological indices obtained from electroencephalography and positron emission tomography, also can be used to investigate some aspects of speech perception.

As in the area of speech production, the past decade has seen important advances in research on the perception of speech. Progress has been notable on many fronts, ranging from improvements in technology to advances in experimental methodologies and theoretical perspectives on the interplay of the factors involved in speech perception and its development.

One important general observation is that rapid development in computer technology during the past ten years has led to numerous achievements in research on speech perception across the lifespan. Remarkable advances in hardware and software, including the development of desktop and laptop computers, have tremendously increased the speed, sophistication and availability of acoustic measurements of natural speech. They have also led to greatly improved techniques for waveform editing and manipulation of speech signals, permitting the generation of high-quality synthesized speech and on-line presentations of speech materials during computer-controlled perceptual testing procedures. All of these capabilities are critical for developing and presenting the carefully controlled speech stimuli that must be used in perceptual studies, whether they involve natural or computer-synthesized utterances. Moreover, whereas the technology required for high quality speech analysis and synthesis was beyond the means of most individual investigators prior to the 1980's, its greater commercial availability and affordability since that time have permitted many more investigators to acquire state-of-the-art equipment in their own laboratories. These improvements have fostered the development of more diverse and sophisticated experimental methods, which have expanded empirical findings on speech perception from infancy through adulthood and have increased the breadth and depth of the theoretical understanding of perceptual processes. To give a few examples, improved computer technology has spurred the generation of connectionist models of perceptual processes, the expansion of cross-language and cross-cultural studies of speech perception in infants and adults and the development of a theoretical model of phonology based on articulatory gestures, which holds promise for enhancing scientific understanding of the link between speech production and perception.

Development of Speech Perception

Since the inception of the field over 20 years ago, the understanding of speech processing in infants has advanced rapidly. Early studies in the field helped to specify the capacities that infants have for discriminating differences in simple speech contrasts, such as the distinction between "ba" and "pa." Further investigations demonstrated that the discriminative capacities of infants under six months of age extended even to speech-sound contrasts not present in the infant's own native language. Moreover, other studies found that infants show perceptual constancy for speech categories; that is, they are able to accommodate the type of variability introduced in the speech signal by changes in speaking rate, vocal pitch and talker's voice. These early studies provided useful information regarding the initial state of perceptual capacities that infants bring to language learning and paved the way for studies that trace the development of these capacities as language is acquired.

Within the past ten years, new information has been gained about the way experience with a native language affects the development of speech perception even during the first year of life. Thus, before they begin to speak, infants have already begun to learn something about the sound patterns of the language spoken by the people around them. The first indications of these changes came from studies that indicated a decline, by about ten months of age, in sensitivity to speech sound differences that are not used to distinguish words in the infant's native language, although the differences may be a meaningful contrast in some other language. Further studies have demonstrated that this decline in sensitivity is particular to certain, rather than all, non-native contrasts. Moreover, recent findings have revealed differences in the way sensitivity to non-native consonant and vowel contrasts changes during language acquisition. Ongoing studies are directed at the factors responsible for the decline in sensitivity to some, but not all, non-native contrasts.

This work is revealing how infants develop the phonologic categories that are used in speaking and understanding utterances in their native language.

Other recent studies suggest that, early in the first year of life, infants begin learning about the characteristic properties and organization of speech sounds in their native language. A comparative study of American and Swedish babies found that, by six months of age, infants' categorization of vowels reflects differences in the organization of adult vowel categories in their native language. Other findings suggest that by nine months of age, infants are able to use information about the way in which sounds are sequenced in their native language (that is, phonotactic properties) to distinguish between native versus non-native words. By that same age infants are also sensitive to sound patterns involving either prosodic or phonetic elements that occur with high regularity in their native language. Sensitivity to such properties may play a role in the development of an infant's ability to segment the stream of speech into sequences of words by providing a sort of "bootstrap" for the infant to discover the boundaries between words.

In a different but related line of research, studies of the nature of speech directed toward infants have led to new and interesting hypotheses about the role that speech perception capacities play in the acquisition of information about grammatical units in the native language. Research in this area has identified potential acoustic markers of grammatical units in the input, such as brief pauses and changes in the pitch contour of the voice. It has also shown that infants appear to pay attention to information marking clause boundaries as early as five months of age and to information about certain phrase boundaries by nine months of age. Other findings indicate that during the first year of life, infants are sensitive to some aspects of semantic and pragmatic information carried in the prosody of native speech.

A number of investigations are under way examining the role of infants' speech perception capacities in learning words and building up a lexicon in their native language. Some studies have looked at how adults present information about new words in speech directed to infants. Other studies have examined the perceptual capacities of infants to detect, attend to and remember the sound patterns of new words.

In addition, many important discoveries continue to be made concerning the nature of basic speech perception capacities in young infants. One issue of continuing interest is the existence of specialized speech processing mechanisms in infants. Studies investigating duplex perception in infants (sounds are heard simultaneously as speech or nonspeech) suggest that speech sounds may be processed differently from nonspeech sounds starting at a very early age. Important new information has been gained about the nature of the information that infants extract and remember from the speech signal.

There are also indications that even during infancy, the processing of speech goes beyond the single modality of auditory information. By 20 weeks of age or earlier, infants show a primitive ability to use visual information about speech. They can detect a match between the auditory presentation of a sound and the sight of the face of a person producing that sound, even when presented with a vowel sound from a foreign language that they have never heard before. Normal adults use speechreading to perceive speech in noisy situations, and research shows that they are strongly influenced, even under good listening conditions, by visual information obtained from the talker's mouth movements. The fact that infants demonstrate simple speechreading abilities suggests that they can already relate audible and visible speech as they watch and listen to adults speak. To the extent that hearing-impaired listeners may rely on visible information when perceiving speech, a better understanding of how speechreading ability develops may ultimately benefit research and treatment efforts aimed at hearing-impaired children.

Despite the great strides that have been made in tracing the origins of speech perception capacities, there has been little research investigating the abilities of young children. The existing studies suggest the gradual refinement of speech processing capacities and of perceived speech sound categories. Some investigations have shown that young children pay more attention to dynamic, as opposed to steady state, aspects of the speech signal. For example, there is a rapid change over time in pitch or other properties of the dynamic speech signal but the properties of the steady state speech signal do not change. There seems to be a shift toward more adult-like performance by the age of seven. Other investigations of phonological awareness indicate a similar trend in the refinement of perceptual categories moving from larger to smaller linguistic units. Such developments are likely to influence reading readiness.

One area of development that has received increasing attention concerns the growth of the lexicon. Studies of children have examined the precision with which words or parts of words are understood and how these representations change as vocabulary grows. One limitation to these studies is the lack of precise information about vocabulary size and content in children at various ages, although children's self-estimates about age of acquisition of particular words have proven useful in predicting experimental outcomes.

An obstacle to research with preschoolers and young school-age children continues to be the lack of adequate methods for testing subjects in this age range. The paradigms that have proven effective with infants and adults often cannot be adequately extended for use with young children and need to be augmented. These gaps in the availability of perceptual methodology parallel similar ones with speech production. It will be important to interweave the evaluation of these two domains in early childhood development, when important changes in the phonological system continue to emerge.

Speech Perception in Adults

Research advances in the past decade have pertained primarily to normal speech perception and although progress has been made, scientists are far from a full understanding of the nature of the speech perception process. One of the most encouraging recent developments has been the effort to tie speech perception processes more closely to other levels of language such as semantics (word meaning), syntax (grammatical structure) and discourse properties (organization of sentences and larger units). This development is evident in the number of studies that have employed natural speech tokens and have tried to examine fluent speech processing and the role of the lexicon in speech processing. As noted earlier, the ongoing improvement and increased availability of new technologies for analyzing, storing and presenting spoken materials have led to their greater use in psycholinguistic research.

Important research continues to be aimed at clarifying the nature of the mechanisms underlying speech perception. The use of new research methods for testing adult perception has enabled investigators to take a different approach to questions about the specificity of mechanisms involved in speech processing. Studies demonstrating that the same acoustic cues can be perceived simultaneously as both speech and nonspeech ("duplex perception") have once again heightened interest in the possibility that special perceptual mechanisms exist for speech processing. At the same time, speech investigators have continued to search for evidence of invariant properties that help listeners identify phonetic elements and articulatory gestures from the acoustic signal. Recent efforts in this domain have examined the role of the dynamic, rather than the static, properties of the speech signal. This shift to exploring the dynamic aspects of the speech signal has led to new studies regarding the way listeners are able to compensate or "normalize" for variation in the speech signal introduced by changes in the talker's voice and speaking rate. Information about how this normalization is accomplished is critical for developing automatic speech recognition devices and may prove useful in aiding individuals who are hearing impaired.

There has been renewed interest in the nature of speech categories. New approaches have helped to provide information about the internal organization of perceptual categories for consonants and vowels. Research on cross-language comparisons and on investigations of second language learners has led to interesting insights about developmental changes in the malleability of speech sound categories in the native language and the extent to which second language learners' speech sound categories resemble those of native language speakers. There are indications that even fluent bilingual speakers may be biased in the direction of processing strategies that are optimal for dealing with one particular language.

Issues concerning the ways in which listeners segment fluent speech into units that reflect linguistic organization (words, phrases and clauses) have sparked a great deal of recent scientific interest. Research on the role that prosodic cues play in segmenting speech has burgeoned. New findings suggest that prosody may aid listeners by clarifying utterances and by marking the onsets of words and phrasal units. In addition, there is evidence of new interactions among linguists, psychologists and speech scientists in this domain, as linguistic models include more perceptual processing considerations. These developments have also proved useful to improving the design of systems for the computer-based automatic recognition of words in fluent speech. At the same time, greater attention is being given to understanding the speech properties that permit listeners to follow a spoken message in background noise. Studies using frequency-modulated sinewave stimuli have helped to clarify the means by which acoustically disparate properties of speech stay integrated in listeners' perception of phonetic information.

Attention is also being given to the study of information processing demands on speech perception. In particular, current studies are examining how variation in the speech signal affects the information handling capacities of listeners. Recent findings indicate that listeners retain a surprising amount of talker-specific information long after their exposure to particular utterances.

The size, number and kinds of processing units accessed by listeners during on-line speech recognition continue to be a source of considerable interest. For example, possible processing units proposed are phonemes, syllables and still larger units such as patterns of rhythm and stress. Findings from cross-language comparisons have suggested the possibility that the size and type of processing unit may vary according to the structural organization of different languages. At the same time, more research is being directed at how the mental organization of the lexicon may affect the speed and efficiency of lexical access. Ultimately, the resolution of issues concerning the nature of processing units will depend on the development of new methods that will effectively tap on-line processing of fluent speech.

Finally, there has been continued progress in the development and refinement of theoretical models of human speech perception. The increased availability of and access to more powerful computational resources have led to increased interest in developing models that simulate on-line speech recognition processes. A number of interesting hypotheses have been advanced concerning the possibility that speech perception processes may be self-organizing, along the lines of connectionist or neural network models of learning. Research investigating the ways in which nonhuman species perceive biologically salient signals continues to provide an interesting point of comparison for the development of theoretical models of the process involved in speech perception by humans.

From a different perspective, the recent development of a theoretical model of phonology that is based on articulatory gestures as the primitive units of phonologic structure may provide insights about the links between perception and production of speech. Another avenue that has begun to provide important information for theoretical models of speech perception is the examination of the neural mechanisms involved in speech perception. Information could be gained through combined studies of perceptual processing and new brain imaging techniques available for assessing regional task-related changes in brain metabolic processes. Convergent information may be obtained through studies of speech perception in populations with known brain damage or neuropsychologic impairments. Current research is beginning to provide some of this neuropsychologic information, but additional efforts in this direction should be encouraged.

Speech Perception and Aging

Research on the general cognitive and perceptual changes associated with normal aging suggests that at least some aspects of speech perception may change with advancing years. For example, the processing of fine-grained temporal information in speech may change with age even when there is no evidence of frank sensory impairment or cognitive decline. Other aspects of speech perception, however, may show little decline with normal aging. After the sixth decade of life, the likelihood increases that there will be some normal age-related (or exposure-related) peripheral hearing loss, perhaps in addition to loss of sensitivity in other sensory modalities, memory loss or some other cognitive decline. The probability of more severe perceptual or cognitive impairments associated with disordered conditions also increases with age. Improved scientific understanding about the effects of normal aging and of age-related impairments on speech perception and comprehension is increasingly important, given trends toward a higher proportion of Americans over the age of 65 and the general lengthening of the average lifespan. However, there is a surprising dearth of research on the effects of normal aging and of aging-related disorders on speech perception abilities. The elderly rank communication difficulties, particularly understanding speech, as one of the greatest problems they experience.

Perceptual Impairments

Speech perception disorders may result from a variety of causes. Peripheral hearing losses attributable to either conductive or sensorineural impairments influence the amount and type of acoustic speech information the listener may pick up. Many critical phonetic properties of speech are carried by relatively brief or low intensity acoustic cues, which may be diminished or eliminated by conductive or sensorineural hearing losses. Research has begun to provide some insights about the effects of peripheral hearing impairments on speech perception, but much remains to be learned about their specific impact on speech comprehension.

Research over the past ten years on the development and technical improvement of cochlear implants for profoundly hearing-impaired individuals has indicated that at least some of the critical information for perceiving environmental acoustic events and speech signals is provided by such devices. Many implant users are able to repeat accurately paragraphs read aloud by an examiner (speech tracking), and some users are able to follow telephone conversations. Results suggest that the perception of the acoustic information provided by cochlear implants may be augmented by the users' ability to make use of speechreading information in face-to-face speech contexts. It also appears that implants provide some users with sufficient acoustic information for them to follow conversation even without visible speech information. Many users, however, fail to achieve these levels of ability, and it is not clear why. Continued improvements in the speech processing strategies employed by cochlear implants have resulted in increasingly accurate speech perception by users.

Hearing losses may greatly interfere with the young child's ability to communicate and to develop language. Some research has evaluated a few aspects of speech perception in children with hearing impairments. However, such studies have been relatively scarce and limited in scope, particularly with respect to longitudinal patterns.

Poor speech perception may also be implicated in a variety of neural disorders and developmental conditions such as autism and dyslexia, as well as after brain injury. Recent studies have begun to elucidate the cognitive, linguistic and speech perception abilities of children with various types of communication disorders. For example, some reports suggest that children with specific language impairments have difficulty with the fine-grained temporal structure of speech. Certain findings indicate that there may be a genetic component to such processing deficits. In addition, longitudinal studies of children with fluctuating conductive hearing losses associated with recurrent otitis media have begun to provide keys to the complex interactive effects of peripheral hearing disturbances on speech perception. However, studies of the effects of both peripheral and central disturbances on speech perception have been relatively limited to date.

Finally, the speech perception abilities of children with functional speech disorders or phonological impairments pose challenges to both scientists and clinicians. It has been hypothesized that the difficulties these children have in mastering the sound system of their language may relate at least in part to an inaccurate perception of critical phonological properties in speech. There have been numerous attempts to evaluate this hypothesis scientifically, but the results obtained so far have not been definitive. There may be a certain subgroup of children with productive speech sound disorders who also exhibit related perceptual difficulties. However, it is not yet known which children will be susceptible to disorders in both perception and production of speech, nor has a determination been made as to the range of children affected or the most appropriate means of assessing and treating such difficulties.

Research on perceptual concomitants of phonological disorders in children has been hampered by the lack of adequate research methods for testing perceptual abilities beyond the age of two years. Indeed, little is known about the perceptual skills of normal children in that age range; thus, no normative database is available against which to compare the perceptual abilities of phonologically disordered young children. The limited research that has been done provides guidelines for further research that should evaluate both perception and production of the child's specific phonological errors and should include self-evaluations of the child's own recorded productions. The self-evaluation approach is suggested by findings that some children both produce and detect in their own speech certain subtle acoustic-phonetic distinctions that adult listeners apparently fail to hear. Further research may determine whether these children develop their own meaningful system of perceptual and productive speech distinctions, which may or may not correspond to the target adult sound system. Research on the speech perception abilities of phonologically disordered children, in general, is likely to carry implications for clinical issues of assessment and treatment of functional speech impairments, as well as to provide important guidelines which may assist in designing appropriate programs for hearing impairments.

Cross Cutting Topics

Multicultural Issues and Research Methodology

Research on speech and language demonstrates the importance of multicultural factors for the appropriate assessment and treatment of speech disorders and for the design of appropriate educational programs. There is increasing recognition of both the need for research on this topic and the usefulness of various research methodologies, such as epidemiologic, longitudinal and ethnographic studies.

Increased attention to multicultural issues produced a rapid increase in information on spoken language characteristics and associated cultural factors for a number of different populations, including African Americans, Hispanic Americans, Native Americans and Asian/Pacific Islander Americans. This knowledge has been disseminated to educators and clinical specialists in an effort to enhance classroom and clinical cross-linguistic and cross-cultural interactions. Although notable progress has been made, there is a serious need for further work in this area.

Important gains have been made in the study of cross-cultural issues in infants and young children. Among the studies in this area are investigations of the effects of exposure to a particular language on early speech perception and speech production in infants. Innovations in research have resulted in new knowledge and have attracted increased research attention to this field.

Program Goals

Speech Production

Basic Structure and Function

Recent advances in the understanding of speech production and in the development of technology for the study of speech have paved the way for a rapid increase in knowledge in this area. Speech is produced with a large number of different tissues that constitute a functional system. The understanding of such a complex system rests on an understanding of the tissues and their interactions. For this reason, biomolecular research on the structures of speech is a high priority. Also needed are histological studies of muscle and nerve cells. Limited information is available on many of the important muscles that regulate events in speech production. Information is also deficient on the biological factors responsible for speech production and speech disorders such as, genetic and epidemiological factors.

One recent and important advance is the expansion of the database to include greater numbers of women and children. Data for adult males have tended to outweigh greatly the data for other gender and age groups, in part because the larger size of the male vocal tract facilitates acoustic and physiologic measurements. Acoustic and physiological methods have been modified to permit extensive studies of the speech of women and children. The expansion of the database is essential to progress in the study of speech disorders that affect women and children. Still needed are data on speech production across diverse racial and ethnic groups to ensure that information on speech is adequate to account for both the general mechanisms shared by all people, and the nature and extent of any multicultural differences.

Although acoustic and physiological methods have been demonstrated as suitable methods to study infant vocalizations, broader application of these methods is needed to realize their potential. The impressive progress in this area is leading to new ideas about the way infant vocalizations such as babbling relate to later speech development. Substantial evidence indicates strong continuities in some aspects of sound production from babbling to early speech. These discoveries hold intriguing potential for early identification of infants at risk for communication disorders. Because vocalization is one of the earliest voluntary motor behaviors to appear, it may aid in the detection of conditions that place infants at risk for developmental disorders or factors that might hinder their cognitive and linguistic achievement.

Sufficient data are now available to permit the development of models of speech production. These models can play an important role in consolidating and guiding scientific progress. Models need to be developed and refined for the individual components of speech production such as the tongue or vocal folds, subsystems such as the respiratory and the overall system of speech production. In addition, models may address different phenomena or types of variables, such as acoustics, aerodynamics, kinematics, neural control, biomechanics, and regulatory functions.

Technological advances have affected essentially every aspect of speech research. However, the potential and limitations of these advances have not been fully realized. There is a need to evaluate the technologies and the measures they provide. In some respects, the capability of technology has outstripped the ability of researchers to evaluate the reliability, validity and effectiveness of measures of speech and voice. Such evaluations are greatly needed. Additional technological advances are still needed for the effective study of speech, for example, methods to examine the simultaneous movements of several articulators.

Speech is central to much of human life, and because speech cannot be isolated from other important human functions, it cannot be studied in isolation. Accordingly, the study of speech production and its disorders touches on a variety of cultural, educational, biomedical and technological factors. Similarly, the program goals for speech production and its disorders cover broad research needs. They range from basic anatomic and physiologic research on the speech production system to studies; on the nature of speech disorders of known and unknown causes; evaluations of assessment and treatment methods; development and refinement of instruments for the study of speech production; studies of multicultural differences in speech; and studies of the interaction of speech production with other capabilities, including speech perception and language formulation.

Disorders of Speech Production

Structurally Based Disorders

Structurally based disorders include acquired defects and congenital anomalies. Acquired defects may be the result of accidental trauma or ablative surgery. These disorders usually impair functions that had been learned and used normally before the insult. Therefore, the goal is to restore function as completely as possible in the face of the structural defect. Congenital anomalies may be monogenic, chromosomal, polygenic-multifactorial or teratogenic. Some are of unknown origin. Genetic research holds important promise for many congenital syndromes that affect craniofacial structures, and this research is strongly encouraged. The assessment and management of congenital disorders also involve considerations of developmental and growth factors, which must be carefully studied in both typically developing children and those with various congenital anomalies.

For acquired and congenital disorders, research is needed to develop standardized assessments, to document the concurrence of various deficits, and to determine the efficacy of treatments. Although it may be possible to locate the defect in a particular structure or set of structures, the effects of the defect can include many aspects of biological, communicative and social functions. Management alternatives for structurally based disorders include surgery, prostheses, behavioral therapy biofeedback and pharmacotherapy. The benefits of these therapeutic methods should be investigated for various types of structurally based disorders and different population characteristics, including age, gender, cultural background and presence of other impairments. This research may indicate differences in efficacy and may also point to improvements that can be made in each management approach.

Neurogenic Disorders of Speech and Swallowing

Motor Speech Disorders. The dysarthrias comprise a group of diverse speech disorders. They vary in underlying neuropathology and in severity and natural course. In addition, individuals with dysarthria vary in level of sensory or cognitive function and may have differing abilities to compensate for their disorder. The diversity of this population dictates the need for careful measures of perceptual, acoustic, physiologic and psychosocial factors relating to the disorder. There is also a pressing need to broaden the scope of study of motor speech disorders to appreciate listener variables that may influence the success of communication and to investigate psychosocial consequences of the disorder. A better understanding is needed of the effects of the various types and degrees of motor impairment on speech adequacy. To develop adequate intervention approaches, understanding is needed of the individual's ability to compensate for various types of impairment. Such understanding could guide decisions about what aspects of speech should be measured in these individuals and could lead to the construction of standardized assessment profiles, allowing information to be pooled from patients at many different centers and clinics.

Swallowing Disorders. Because of the growing realization that the type and extent of swallowing disorders vary among individuals, there continues to be a need to develop comprehensive test batteries including measures of functional performance and apply them to various populations. Studies also are needed to understand the complex interactions among the various aspects of the swallowing mechanism and to understand its relation to speech function. Because intervention in swallowing disorders is becoming an increasingly important clinical activity, there is a need to document the impact of that intervention both in terms of the physical aspects of swallowing and functional outcomes. For example, research is needed on the relationship between the underlying pathophysiology and real-world situations such as eating and drinking.

Stuttering

In a review of the current state of basic and clinical research on stuttering, four issues emerge which focus on specific aspects of stuttering theory and treatment. First, more needs to be known about the onset and development of stuttering in children because this information provides a large part of the knowledge base from which improved theories and treatments can be developed. Second, speech production characteristics and abilities and associated nervous system activities need extensive study since it is dysfluent speech production that clinicians must ultimately be able to assess and change to increase speech fluency. Third, despite a wide variety of therapy regimens available, little is known about numerous salient therapeutic issues, such as the relative efficacy and effectiveness of treatments for stuttering, particularly in terms of short-, medium- and long-range recovery. Systematic descriptive and experimental work is needed to understand and eventually improve diagnosis and treatment of stuttering. Fourth, basic as well as applied insights into stuttering could be obtained through the study of related problems, such as acquired stuttering (that is, stuttering that typically begins after childhood as a result of injury or disease), as well as through the application of newer technologies, such as artificial neural networks, to study stuttering. Pursuit of these four research issues should improve the diagnosis and treatment of stuttering so that individuals who stutter have maximal opportunity to reach their personal academic, social and vocational goals.

Articulation and Phonological Disorders

Articulation and phonological disorders affect a significant number of preschool and school-age children. It is also well-documented that adults who had disorders as children continue to have difficulties processing phonological information, especially in reading and writing. These difficulties can broadly affect educational, vocational and social opportunities. The long-term consequences of phonological disorders, especially in the linguistic domain, must also be investigated. The relationship between higher order linguistic skills, such as reading and writing, are important topics to consider. Of related interest is the study of the familial incidence of functional speech disorders. Retrospective and prospective investigations will help identify the genetic bases of speech disorders and will identify those children who may be seriously at risk for speech disorders.

Research is needed to address issues of identification, assessment and treatment of articulation and phonological disorders. First, descriptive research on the course of phonological development in English and other languages must be continued, particularly from a lifespan perspective. For example, suitable bases of comparison with normal development must be established for a wide range of acoustic-phonetic distinctions. Current technology must advance to allow for the acoustic-phonetic evaluation of children's speech that does not rely on models of the adult vocal tract but on appropriate information about the child's vocal tract. These findings will contribute toward our understanding of the course of normal sound learning and will help to isolate the universal linguistic and motor components of sound systems. This information will have implications for theories of language development. Also, a cross-language perspective is especially important, because it will provide a valuable database for use in the assessment of children from multicultural backgrounds. Second, research on potential subgroups of phonological disorders is needed. This work will characterize commonalities among children with phonological disorders, as well as identify the expected range of variation in this population and its subgroups. This information will contribute to the identification of predisposing factors. Third, assessment batteries must be developed within contemporary theoretical frameworks of linguistics and cognitive and developmental psychology. These measures must be sensitive to multicultural populations. The accurate assessment of phonological disorders will contribute to efficacious treatment, the fourth area. Only a small handful of treatment paradigms have been experimentally evaluated to date. Therefore, treatment research is not only needed in the evaluation of existing procedures, and in the development of new treatment methodologies. Treatment procedures that make use of the most current technology and that focus on perception and production of speech are especially warranted.

Speech of Persons Who Are Hearing Impaired

Audition plays an important role in the development and maintenance of speech production capabilities. A thorough understanding of the role of auditory feedback on speech production requires a lifespan research perspective. A common assumption regarding the role of auditory information in early speech development in children is that this information is particularly important during a hypothesized critical or optimal period. Research is needed to demonstrate the effects of different degrees of hearing loss during this period. Studies are needed to elucidate how hearing-impaired children interact with others in developing speech production, how others interact with them as they develop speech, how they monitor themselves and self-correct, and how various assistive devices influence the interplay between speaker-listener pairs and self-monitoring. An understanding of this developmental period, as well as the entire lifespan, requires sensitive and efficient measures that are suitable for the investigation of speech production capabilities in the child or adult with hearing impairment. It is also important to study the relationships between the use of manually coded English and the development of speech production in persons who are hearing-impaired.

Many different types of assistive listening devices are available to persons with hearing impairment. Much more needs to be known about these devices and their effectiveness for different users who vary in age, degree and onset of impairment and other characteristics. The optimum use of these devices requires knowledge about user candidacy, type and amount of training and other aspects of clinical management. For both children and adults with hearing impairment, it is particularly important to identify interventions that promote speech intelligibility. Meeting this objective will require reliable and valid measures of intelligibility that can be used throughout the lifespan and with different clinical interventions.

More effective speech training tools are needed to assist individuals who are hearing impaired and who desire to learn more accurate speech production and self-monitoring. Computer-based training systems with visual displays of acoustic or physiologic patterns need to be evaluated as possible tools for expanding the range of instruments available to clinicians to teach speech production. Investigations are needed to determine the effectiveness of such tools for maximizing performance and for comparing relative effectiveness with other tools.

Augmentative and Assistive Systems

As devices for augmentative and assistive communication are more commonly used in a variety of settings, several areas of concern have emerged. First, further information is needed about the natural development of speech, language and social interaction of persons using these systems and the influence of device or technique characteristics on the rate of learning in these areas. Clinical differences should be empirically investigated in light of new theories from normal development examining the interaction among all of these aspects of development. Second, more extensive study is needed of the characteristics of successful users, including users with a variety of physical, cognitive, language and sensory skill impairments. This information would provide a basis for determining maximum performance based on data from persons with impaired speech and learning skills. Third, extensive research is needed on developing and testing the relative efficacy of treatment models. Although several such models have been developed for treatment within related areas of speech-language impairments, these models have not been sufficiently adapted for treatment.

Efforts are needed to understand the different populations who use augmentative communication devices in terms of their motor, linguistic and cognitive capabilities and the settings in which they use communication systems. This understanding will guide device development. Information is also needed about the demands placed on the users in an effort to develop system selection and training programs that will ensure optimum use. Short-term and longitudinal studies are needed to determine whether one type of device or a combination of devices can improve speech intelligibility.

Since these devices provide very different types of feedback information, investigators must question whether current speech intervention strategies are appropriate or whether new strategies should be developed. Thus, treatment efficacy studies investigating the interplay between sensory feedback and speech development are critical. It is not clear how the acquisition of speech is influenced by information provided by cochlear implants, tactile aids, hearing aids or visual information provided by speechreading. Nor is it clear how speech patterns developed and trained with one type of device might be influenced by a different device acquired at a later time. This issue is especially critical as some devices, such as cochlear implants, are restricted to children two years of age and older; yet, current clinical practices provide hearing and tactile aids to younger children. Cochlear implants are quite expensive and candidates may be delayed in obtaining implants.

Speech Perception

The program goals for speech perception and its disorders are to support research that will enhance scientific understanding of normal speech perception across the human lifespan and the effects of auditory and other disorders on speech perception. To meet these goals, research should focus on the interplay of factors affecting early development of speech perception and on perceptual organization and its underlying processes in adults. Additional knowledge is also needed on the effects of normal aging and on the extent to which the perception of speech is affected by various types of hearing impairment and phonologic and communication disorders.

Early Development

Research with infants and young children should be encouraged for a fuller understanding of the role that basic speech perception capacities play in the acquisition of a native language, including the development of word meanings (semantics), the acquisition of grammatical units (syntax) and comprehension of larger units (discourse properties). Studies are needed to help elucidate the structure and content of the categories that infants and children rely on in perceiving speech and to help determine the nature and malleability of categories as languages are acquired. More knowledge must also be gained on how infants and young children develop the ability to process fluent speech, especially the ability to segment speech into words and to cope with talker variability and speech in noisy environments.

Research should delineate the neurophysiologic basis for speech perception capacities and their development during language acquisition. Studies on this topic should employ both traditional and recently developed techniques of measuring metabolic activity (positron emission tomography) and mapping electromagnetic activity of the brain.

At the same time, it is also important to obtain complete information about the characteristics of speech input critical to the development of fluent speech perception of utterances in the native language. Research must be encouraged on modeling developmental changes in the speech perception processes, especially the development of phonological knowledge.

Studies on the relationship between sign perception and speech perception development should be conducted to further scientific understanding about whether the developmental growth of language processing is similar regardless of the modality of acquisition.

There is a need for developmental research that will lead to understanding the impact of interacting knowledge sources ,including information available from different modalities and at higher levels of linguistic and cognitive organization.

Adulthood

Research on speech perception in normal adults depends in a large degree on characterizing the basic properties of speech. Program goals include identifying perceptually important acoustic and articulatory variables, how they are integrated in perception and how they may vary as a result of linguistic experience and listener-speaker characteristics. For example, individual variation and special populations such as people with specific speech disorders or adults learning English as a second language.

Additional research is needed to define how speech perception relates to higher levels of language, including vocabulary (lexicon), word meaning (semantics), grammar (syntax) and sentence and narrative comprehension (discourse). Based on the findings of investigations into these factors, theoretical work should also be fostered to develop more comprehensive models of speech recognition, including models that derive linguistic structures from spoken utterances, models of auditory perception as they pertain to speech and computer simulation models of speech processes.

Recent research interest has examined the influence of specific language experience on speech perception. Further work is needed to characterize the perceptual differences that may arise from the acquisition of different languages and dialects. The results should help delineate the changes in perception, including those for segmental and prosodic information, that may occur when new languages and dialects are learned.

Another important direction of speech perception research is the study of on-line speech recognition processes to develop a more complete understanding of the role of higher level cognitive and linguistic knowledge in the perception of fluent speech. This research approach and others related to speech perception in adults will require investigations that will further delineate the range of variability in speech perception. Differences in cue weighting and integration and variations in reliance on information obtained by different modalities should be included. This information will provide insight about the factors leading to individual variation, including multicultural and gender differences. It will help relate such variation to speech comprehension in ideal and nonideal listening conditions, second language and dialect learning and possible responses to hearing loss in later life.

Aging

Additional studies based on recent experimental findings on adult speech perception are needed to investigate speech perception skills in the elderly and following gradual or sudden hearing loss or brain damage. It is especially important to examine perceptual difficulties in the elderly who are experiencing cognitive deficits as in Alzheimer's disease and in people experiencing multisensory losses as in loses of hearing and vision. Furthermore, it is necessary to determine whether changes in speech perception occur with normal aging and, if so, to assess the extent they affect language comprehension skills.

Perceptual Impairments

More extensive research is needed to examine the effects of hearing impairments on speech perception, especially in early development. Such work should include evaluation of the effects of hearing aids and cochlear implants on speech and language development in children who are hearing impaired or deaf. Research is also needed to evaluate the extent speech perception capabilities are involved in or affected by phonologic disorders and communicative or cognitive impairments. It is important to examine the psychoacoustic correlates of speech perception and to determine how hearing loss influences psychoacoustic and speech perception performance. Further research is needed to clarify the relationship between various hearing losses and the aspects of speech perception that are most affected. Research should explore the relationship between language ability and hearing impairment. For example, studies are needed that delineate performance differences associated with age of onset of hearing loss that is, pre- versus post-language hearing loss. Such information will be important for improving the properties of hearing aids to provide the best advantage for the perception of speech. In addition, this information may be useful for laying the foundations for intervention-efficacy studies to explore how to help individuals cope with hearing loss. Research on the relation between the acoustic information conveyed by cochlear implants and hearing aids and the resulting changes in speech perception ability will be critical to provide understanding of how the devices can be designed to optimize speech perception by users who are profoundly hearing impaired.

Cross Cutting Topics

Research Methodology

These various research goals should be pursued with careful attention to research design to achieve maximum value. Particular emphasis should be given to measurement standardization, epidemiologic research, longitudinal studies and ethnographic investigations.

Research on speech perception and speech production should be considered within a research design framework that encompasses two important factors. First, the work should be undertaken with a view toward a developmental, lifespan perspective. This perspective recognizes that speech perception and production do not occur in a vacuum but rather that biological, psychological, and social factors act independently and in relationship with one another to influence development, disorder and response to intervention. Second, for optimal scientific benefit, research in speech perception and production should be conducted within a clearly articulated and empirically based, theoretical model that reflects putative underlying processes.

Careful attention should be given to the instrumentation and procedures used in measuring speech perception, speech production and the disorders associated with each. One key problem involves the reliability and validity of instruments. Reliability is the accuracy or precision of a measuring instrument; without adequate reliability, results cannot be meaningfully interpreted. Validity is the ability of the instrument to measure the intended underlying constructs and is closely related to derivation and empirical testing of hypotheses based on the underlying theory. In addition, the identification and operational definition of psychosocial and biological risk factors and correlates should be undertaken with as much care as the outcome definition, especially when describing relevant subgroups. It is as important to attend to the reliability and validity of risk factor assessment as it is to the reliability and validity of outcome assessment.

There is a continuing need for various data from representative samples of normative and disordered populations, with such data having sufficient statistical power to demonstrate significant differences between subgroups. Appropriate populations can be identified through descriptive and analytic epidemiologic studies. These studies define the population in terms of its sociodemographic characteristics, such as age, gender and educational achievement, and even more importantly, in terms of other risk and protective factors. Additional research is needed to identify and understand the biological foundations of speech disorders and subtypes using such techniques as molecular genetics and familial studies. Being able to characterize the study population is essential in identification of subgroups, for example, individuals with co-morbid conditions, since these groups may have disorders with different causes and may vary in their responses to treatment. These methodological concerns are especially important for evaluation of the numerous factors associated with specific disorders, including academic performance, school drop-out rates, employability and continuing education and training in a changing job market. These and other broader social and educational factors are particularly important to address in studies on multicultural influences on speech function and disorders. Given the increasing theoretical and applied interest in cross-language studies of speech development and disorders, there is a need to foster the establishment of international networks that can increase the sharing of information and databases across cultures and language groups and improve the potential of scientists to engage in international collaborations.

Multicultural Issues

As awareness of the cultural diversity within the United States increases, there is a corresponding increase in the challenges and opportunities associated with a multicultural population. Because speech patterns are strongly affected by cultural background, studies on speech are an important element of multicultural research. Of course, such studies hold particular significance for the assessment and treatment of speech disorders in individuals from various cultures. But in addition, cultural differences in speech and language are important considerations in education, health care, vocational pursuits and general, social participation. Basic research on multicultural differences in speech, therefore, should be fostered given its manifold implications. Clinical research should address multicultural differences if the information is to be applied to a culturally diverse society. Speech and language often are key factors in multicultural studies, and although information in this area has burgeoned, more needs to be learned to support effective educational and clinical progress.

Multicultural issues should be explored in every speech disorder. The available information is too limited in scope to ensure effective assessment and treatment of speech disorders for various cultural groups within the population of the United States. Knowledge sufficient to inform clinical practice will require the application of various research methodologies, including longitudinal and culturally sensitive epidemiologic research, as well as the study of associated factors such as academic and job performance of the individuals affected.

Research Opportunities

Speech Production and Its Disorders

Basic Structure and Function

Several different kinds of research are needed on the anatomy and physiology of speech to:

- Study vocal tract morphology and dynamics in large numbers of subjects and use the data to develop articulatory models.
- Study cell structural and functional properties to understand better the characteristics of orofacial muscle tissue in health and disease.
- Examine the sensory mechanisms associated with the orofacial region from the structural, physiological and psychophysical perspectives.
- Study the neural mechanisms underlying voluntary control of orofacial structures in experimental animals.
- Study the coordination among speech articulators and subsystems by simultaneously collecting data on articulatory, laryngeal and respiratory events during speech, and use the resulting evidence to develop comprehensive models of speech movement control.
- Study human central nervous system function in relation to speech production using available noninvasive procedures.

Lifespan Studies

It is important to provide a more detailed description of the gestural aggregates used in forming speech sounds, to delineate and model the control processes that underlie speech movements and to describe and model how changes in underlying control processes may change over the lifespan. Research needs are as follows:

- Use refined perceptual, acoustic or physiologic techniques to investigate the detailed changes that occur in the vocalizations of typically developing infants. The resulting data are necessary for understanding normal speech development and interpreting similar data from infants judged to be at risk for speech disorders.
- Compare the vocal development of infants raised in different language backgrounds to determine the timing and nature of language-background influences on speech development.
- Collect detailed data on the vocal development of infants judged to be at risk for speech disorders.
- Identify the bases and underlying control principles for orofacial, laryngeal and respiratory actions as infants make the transition from babbling to first words.
- Study various aspects of speech production from infancy through childhood. Data on developmental changes in acoustic, aerodynamic, kinematic and linguistic properties should be incorporated in developmental models of speech production.
- Describe how advances in spoken language during normal development are associated with changes in motor control of speech.
- Develop for males and females normative databases for acoustic, aerodynamic and kinematic measures of speech production from infancy through the advanced years.
- Use imaging methods to study developmental changes in vocal tract anatomy in order to assemble a vocal tract atlas for males and females of different ages.
- Determine the biomechanical accompaniments of growth, maturation and senescence in the speech production system.
- Determine, throughout the lifespan, the effects of toxic exposure, mechanical trauma, and neurogenic damage to the tissues of the speech production system.
- Examine in detail changes across the lifespan in performance characteristics of the speech articulators, such as speed, acceleration, range of motion, strength, fatigability and also pressure and phonatory regulation in both speech and nonspeech oromotor tasks.
- Extend earlier studies of speech motor control and phonological performance to a more ecologically valid body of utterances, for example, real single words spoken

spontaneously and utterances that are sufficiently long and complex to stress memory and cognition.

- Elucidate changes across the lifespan in extent and magnitude of coproduction (coarticulation) of phonetic segments within larger units of speech (words or phrases) and relate these changes, where possible, to changes in the perceptual representation of the lexicon.
- Account for the slowing of articulation observed in elderly populations in terms of neurogenic and muscular changes.

Modeling

Research needs are as follows:

- Continue to develop theories of speech production processes that incorporate new theoretical developments from related disciplines.
- Develop and evaluate models for individual components and subsystems of speech production. Because the entire system of speech represents complex anatomy and physiology, progress will depend on an increased understanding of the system's various parts.
- Develop and evaluate physiologic and acoustic models of speech production that can be applied to a wide range of issues in normal and disordered speech.
- Continue efforts to solve the one-to-many relation between acoustic signal and vocal tract configuration, and evaluate progress with a diverse population of speakers.
- Attempt to use new information about central nervous system functioning (brain imaging) to propose new models of neural control of speech and other behaviors using the same musculature.
- Extend or apply recent advances in linguistics, information processing, communication engineering, artificial intelligence and allied fields to problems in speech production and perception.
- Modify existing models of speech production to extend their relevance to a broad population of speakers (both genders, various ages and of diverse physical sizes).

Technology

Research on speech production has been greatly facilitated by recent technological advances. The application of these advances holds potential for a rapid growth in the understanding of speech production. Research is needed to:

- Foster the development of new technological systems for the acoustic and physiologic study of speech. The need is especially great for systems that can be used with speakers of either sex and of varying ages.
- Evaluate existing technological systems and measures to determine their validity, reliability and efficiency. A number of quantitative indices are now available for the study of speech and its disorders, but the relative merits of these measures have not been systematically evaluated.
- Continue to develop and evaluate noninvasive procedures for imaging the vocal tract and monitoring movements of the speech structures.
- Improve the capability for the simultaneous monitoring of respiratory, laryngeal and articulatory events in speech production. This technological capability is critical to the understanding of interactions among the components of speech production.
- Apply brain imaging techniques to the study of the neural events associated with various tasks of speech production and perception.
- Continue developing technological systems for speech synthesis of various types. Terminal analog synthesis has been highly successful in generating speech stimuli for perceptual experiments and other purposes, but refinements are needed to make synthesis systems flexible and easy to use. Articulatory synthesizers are needed to model the relationship between structural movement and acoustic output.
- Develop and apply procedures of machine speech recognition for a diverse population of speakers, including children, men, women and speakers who differ in speaking rate, dialect, disorders or other features.
- Explore the clinical application of speech synthesis and speech recognition devices, including their incorporation into augmentative and assistive systems for those with severe speech impairments, as well as for the development of well-defined strategies for assessment and intervention.
- Develop and evaluate algorithms and procedures to study the relationship between perceptual ratings of speech and various acoustic and physiologic measures of speech activity.
- Refine computer-based methods for the collection of phonetic and phonologic data, which may be coordinated with acoustic or physiologic analyses.

- Explore the application of expert systems to the assessment and management of various speech disorders (i.e., toward improvements in augmentative and assistive systems).

Disorders of Speech Production

Structurally Based Disorders

The following research opportunities are indicated for both acquired defects and congenital anomalies:

Acquired Defects

- Optimize treatment outcome through more consistent documentation of speech production skills in the premorbid state, postablative state and posttreatment state, with longitudinal study of stability of treatment results. (Although innovations in surgical and prosthetic treatment are reported on a continual basis, relatively few of the reports contain adequate documentation of speech production. In many reports, assessments consist solely of global judgments).

- Evaluate the interaction of treatment with all possible concomitant areas of deficit including hearing, cognitive status and language.

- Foster development of standardized assessment protocols.

- Develop treatment efficacy data, including comparative cost-benefit data on both physical management (surgical and prosthetic) and speech treatment.

Congenital Anomalies

- Expand the knowledge base regarding prevalence of specific types of communication disorders in multiple anomaly syndromes. The purpose is to prepare clinicians and families to deal with expected areas of deficit in individuals with known syndromes; and conversely, to add to the phenotypic spectrum of recognized syndromes so that diagnosed communication disorders may be used as possible indications of the presence of these syndromes. This effort must take into account both individual variation and the range of syndromic expression.

- Expand the database regarding development of infants with congenital anomalies, with specific emphasis on prelinguistic development, early differences in communication development (including response to treatment) and long-term development (including stability of results).

- Encourage continued research into the use of instruments such as the electropalatograph to improve the efficiency of articulation therapy.

- Encourage research on the effects of early versus late intervention and coordinated interdisciplinary team care versus compartmentalized care.
- Develop longitudinal and cross-sectional data regarding response to treatment in individuals who are from developing countries and who have untreated or inadequately treated cleft palates. Specific areas of concern include compliance with treatment recommendations and acquisition of a new phonological system (English) with an "altered" speech production mechanism (repaired velopharyngeal system).

Neurogenic Disorders of Speech and Oral Motor Function

The following research opportunities are identified for neurogenic disorders of speech and swallowing:

Motor Speech Disorders

- Develop standardized assessment profiles for neurogenic disorders, based on perceptual, acoustic, physiologic and psychosocial data, which, taken together, will provide a firm basis for understanding impaired functions including respiration, phonation and articulation.
- Determine how motor speech disorders are affected by individual characteristics such as age, gender, general health and psychological status.
- Examine the relationship among various aspects of the disorders, including the relationship between respiratory function and oral articulatory precision in individuals with various types and severity of motor speech disorders.
- Study task and instructional variables that affect speech performance of individuals with a variety of disorders and at various stages of progression of the disorder.
- Investigate the quality and severity of speech motor impairments that often accompany conditions such as aphasia, dementia, traumatic brain injury and affective or other psychiatric disorders.
- Study changes in speech performance longitudinally in individuals who are either recovering from or experiencing progression of motor speech impairment.
- Examine the abilities and strategies of individuals to compensate for motor speech impairment.
- Examine variables related to listeners' perception of dysarthric speech and the influence of listener

variables and characteristics on judgments of speech intelligibility.

- Assess the impact of motor speech disorders on the psychosocial function and quality of life of individuals who experience these disorders.
- Compile normative data related to aging and speech production.
- Investigate the use of computer recognition of dysarthric speech with the goal of automatic recoding and synthetic output.
- Study the relationship between perceptual ratings of speech abnormality and measures of the acoustic and physiologic events of speech.
- Assess orofacial sensory function and speech perception in individuals with dysarthria.
- Study the efficacy of various interventions for dysarthria and the factors that contribute to candidacy for such intervention.

Swallowing Disorders

- Evaluate changes in the pattern and severity of swallowing disorders over time in individuals with either progressive or diminishing swallowing disorders of various causes.
- Examine functional swallowing abilities in individuals with various types and severities of swallowing disorders and relate these functional outcomes to the nature and extent of the underlying pathophysiology.
- Examine the mechanism of aspiration pneumonia and variables that relate to its occurrence so that data related to aspiration can be used in "at risk" equations.
- Study the relationship between pharyngeal and esophageal function in individuals with various types and severities of swallowing disorders.
- Develop improved assessment protocols, drawing on available methods such as videofluorography, manometry, electroglottography and ultrasound imaging.
- Study orofacial sensory function and respiratory function in individuals with swallowing disorders.
- Study the population of elderly and institutionalized individuals at risk for swallowing disorders and determine the consequent nutritional and medical problems.

- Study multicultural considerations relating to dysphagia treatment, such as dietary habits and proscriptions.

- Study the efficacy of various interventions for swallowing disorders and the factors that contribute to candidacy for such intervention.

- Investigate the effects of swallowing disorders on speech functions.

Stuttering

Onset and Development of Stuttering

Stuttering, for the vast majority of individuals, is first observed in childhood, typically before seven years of age. Despite this fact, relatively little is known about basic aspects of childhood stuttering, for example, its relationship to developments in phonology and language and the relative influence of parent communication behavior. Research is needed to:

- Study the onset and development of speech dysfluency in nonstuttering children, particularly between two and six years of age.

- Study the parallel development of speech dysfluency, phonology, expressive and receptive language and cognitive development in children who stutter and those who do not, particularly between two and six years of age.

- Study the relationships among intelligibility, phonological processes, articulation errors and speech dysfluencies in children who do and do not stutter.

- Study sources of acoustic, physiologic, perceptual and behavioral heterogeneity among children who stutter, as a prelude to the objective assessment of subgroups, behaviorally and etiologically.

- Study the relationship between overt repairs, covert repairs, speech errors and speech dysfluencies in young stutterers and nonstutterers' conversational speech.

- Study the relationship between speaker and listener speaking rate, response time latency and simul-talking (listener's speech overlapping in time with speaker's speech) and speech dysfluency in stutterers and nonstutterers.

- Study mothers' and fathers' nonspeech behavior in association with their children's dysfluent speech, particularly the time course of parent and child nonspeech behaviors during the child's fluent and stuttered speech.

- Study the nonspeech behavior as a possible indicator of the child's development of awareness of speech behavior and errors in this behavior.

Speech Production and Related Issues

Stuttering is first and foremost a disruption in ongoing, fluent speech production, and yet there is much that is unknown about the speech production associated with dysfluent speech in persons who stutter. Research is needed to:

- Examine the number and nature of subtle aberrations in speech production, particularly as they may relate to behavioral symptoms and risk factors for continued stuttering in children.
- Study tremor as it may manifest itself in respiratory, phonatory and articulatory structures and muscles, particularly as it relates to the onset, development and occurrence of stuttering in children.
- Study the number, nature and time course of speech production events associated with instances of stuttering in children and adults.
- Study the relationship between stuttering, self-reporting of anxiety, autonomic arousal and other nervous system functions.
- Study the relationship between simple and complex manual and speech timing tasks, autonomic arousal and disruptions in rate, precision and sequencing of these tasks.
- Study the possible genetic transmission or inherited predisposition for stuttering, in individuals exhibiting a stuttering phenotype which is based on objective, well-defined and replicable criteria.

Diagnosis and Treatment

Although preschool and school-age children, teenagers and adults who stutter often receive therapy, much is unknown about a variety of important issues in this area. For example, do intensive (several hours each day for several weeks) versus extensive (one or two hours per week for several months) treatments lead to more resistance to relapse? Additionally, do children who stutter and exhibit other problems take longer to improve and relapse more than those without other problems? Investigations should:

- Study the treatment efficacy of standard therapeutic regimens on changes in stuttering as well as relapse in changed stuttering in children with and without concomitant communication problems such as expressive language disorders or delays.
- Study the naturalness of speech behavior associated with changes in speech fluency that result from

various standard therapeutic regimens.

- Study children who stutter for acoustic, physiologic and behavioral events, including age of onset, that indicate that the child may be at risk for continued, chronic stuttering.

- Study the effects of time-out procedures on experimenter's or clinician's speech rate, length and complexity of utterance, response time latency and any associated change in stuttering.

Related Issues

Stuttering or stuttering-like behavior sometimes appears in later life or after trauma or disease (acquired stuttering). Research is needed to:

- Assess differences between those who stutter and nonstutterers in biochemical parameters including serum levels of cations (magnesium) that may affect neurotransmission during nonspeech and speech tasks.

- Study the onset, development, number and nature of symptoms associated with acquired stuttering and compare them with similar events associated with developmental stuttering.

- Study the acoustic, physiologic and behavioral characteristics of stuttering-related phenomena such as word retrieval difficulties and develop explanatory models to account for similarities and differences between stuttering and such phenomena.

- Study the influence of frequency and accuracy of self-detection of speech errors on ongoing speech fluency. This information should be useful in the development of models of dysfluency. General studies are needed on the speech perception abilities of children and adults who stutter.

- Encourage improved perceptual as well as automated means for identifying stuttering, classifying people who stutter and reliably and validly determining risk factors for continuing stuttering.

Articulation and Phonological Disorders

Research on a variety of topics pertaining to phonological development, phonological disorders and phonological characteristics of multicultural populations is needed to:

- Identify possible sources and domains of disruption in the sound system of language, with broad and interdisciplinary examination of the linguistic, cognitive, motoric, perceptual, neurogenic, genetic and biologic bases of the disorder.

- Delineate potential subgroups of phonological disorders with appropriate techniques for the differential diagnosis and effective treatment of these populations.

- Extend the study of phonology and phonological disorders to encompass a speaker's entire lifespan.
- Determine cross-linguistic acquisition and organization of sound systems to use as a baseline for the diagnosis and treatment of disorders, and also determine the range of normal variation in the development of linguistic systems.
- Isolate the basic units of phonologic systems, determine their nature (acoustic and articulatory) and characterize how they may change with development.
- Obtain more complete information about components of developing phonologic systems that may be susceptible to disruption, including potential disturbances in the acquisition of vowels, suprasegmentals and sound changes associated with morphology.
- Develop, evaluate and standardize phonologic assessment procedures based upon current theoretical models of speech production, speech perception and cognitive development.
- Promote improvements in the treatment and monitoring of phonological disorders, particularly in children from multicultural populations.
- Encourage the clinical evaluation of theoretically motivated treatment paradigms within a developmental perspective, including clinical trials with children who may have different patterns of sound disorders.
- Explore the possible utility and effectiveness of treatment paradigms across populations, including second language learners and persons with hearing impairments.
- Track the long-term efficacy of phonological treatment and identify potential factors that may contribute to regressions in learning or lack of retention over time.
- Study the relationships among child head injury, school failure and speech disorders.
- Evaluate the social, educational and employment consequences of phonological disorders. Include the possible associative relationships to lack of or not completing education, unemployment, delinquency and dialect, throughout the lifespan using retrospective and prospective studies.

- Foster investigations of the acoustic-phonetic evaluation of speech in children that relies on characteristics of the developing vocal tract.

- Characterize further the acceptable range of variation in development of acoustic-phonetic properties of normal speech in children.

- Define the relationship between phonological development and other linguistic skills, such as reading and writing.

- Study the occurrence and type of speech articulation disorders in populations with neural and genetic deficits, such as cerebral palsy or mental retardation.

- Explore the relationship between disorders of speech and language, including phonology and its concurrence with voice, expressive language and hearing impairment.

- Isolate the range of factors contributing to intelligibility of phonologically impaired speech and explore applications to speech synthesis and recognition.

- Establish criteria for differentiating clinically relevant phonological and articulatory variation from normal language differences across cultural groups.

- Extend and enrich the existing descriptions of the acquisition of English phonology. Accounts of phonological development will chart the orderly additions to and changes in the inventory of phonetic and phonemic (contrastive) sound units, as well as changes in or additions to processes and rules that operate on words and smaller linguistic units.

- Extend existing work on English to nonstandard dialects of American English and to other languages that are spoken in the United States.

- Determine the relationship between phonological acquisition and other aspects of linguistic and cognitive development.

- Determine what role early bilingualism plays in the rate of acquisition and eventual adequacy of phonological control of the native language and chart changes in the individual's ability to master the production of second dialects and languages throughout the lifespan.

- Assess the perceptual consequences, for example, decrease in intelligibility of various divergences from the norms of standard English, such as application of phonological processes or inventory limitations, both typical and atypical. Such work should target the speech of children learning English as a native language, as well as individuals of various ages who are acquiring English as a second language.

Speech of People Who Are Hearing Impaired

Research opportunities encompass many issues and needs, as follows:

- Conduct studies of the effects on speech production of hearing loss at different stages of life.
- Delineate the speech production potential and hearing status of hearing-impaired infants and young children, noting the differences that might occur in children who are hearing impaired from birth versus those acquiring a hearing loss later in life.
- Investigate the speech production characteristics of children with various degrees of hearing impairment, including mild, moderate and severe hearing losses. Data from such studies may serve as population-typical data predicting speech performance in young children who are hearing impaired. They may also serve as benchmark performance measures for children using assistive listening devices, such as tactile aids, hearing aids or cochlear implants.
- Improve speech training aids to deliver articulatory information in a well defined manner and to assess learning independently for different components of the articulatory system.
- Examine the effects of the techniques used to train speech production skills in persons who are hearing impaired.
- Investigate the change over time in the influence of tactile aids, analog and digital hearing aids and cochlear implants on speech production in children and adults.
- Examine the speaker-listener interactions involved in communication with speakers who are hearing impaired.
- Explore the speech production characteristics of adult speakers with sustained hearing impairments after speech is developed, adults with intelligible speech but longstanding hearing losses and adult users of cochlear implants.
- Investigate factors that cause major effects on the intelligibility of the speech of individuals who are hearing impaired as a function of educational history, residual hearing and communication mode.
- Develop methods to improve overall speech intelligibility in individuals with various degrees of hearing loss.
- Explore intervention strategies for developing intelligible speech for

interested individuals who are hearing impaired using either predominantly oral systems or combinations of communication systems.

Augmentative and Assistive Systems

Research opportunities in the area of augmentative and assistive systems include the study of user characteristics, device properties, user-device interactions and social-communicative effectiveness. Particular opportunities are as follows:

- Conduct real-world studies of the characteristics of clinical populations who use augmentative communication, their interaction with existing devices and unmet needs. The results of such studies should guide device development.
- Study the demands in using augmentative devices, including cognition, literacy, linguistic and pragmatic function requirements of successful use. An understanding of these demands will lead to appropriate device selection as well as to the development of suitable training regimes. It is important to address the development of skills needed to use these devices as well as the variations in device performance in different conditions.
- Study the integration of natural speech with the use of augmentative communication devices.
- Examine the role of partners and partner training in the use of augmentative communication.
- Examine the augmentative communication needs of individuals on ventilators.
- Use current knowledge about speech perception to guide investigations of computer speech recognition as a means to computer access for individuals with severe impairment of speech and hand function.
- Compare and contrast the social acceptability of various features of augmentative communication devices including the various "voices" (e.g., male and female) employed in speech synthesis and provisions for adjusting rate or emotion.
- Study the intelligibility of systems that provide a speech output and identify means for improving intelligibility, based on current knowledge about natural speech acoustics and influences on intelligibility.
- Develop and evaluate treatment models for augmentative and assistive devices.
- Investigate similarities and differences in the capabilities of

speakers and nonspeakers in relation to communication patterns and settings.

Speech Perception and its Disorders

Early Development

Native Language Development

To understand the role basic speech perception capacities play in the acquisition of a native language, more information is needed about the universal abilities of young infants to perceive speech properties at various levels in the speech signal (phonetic, prosodic and syllabic) and about the developing influence of the ambient language on infant speech perception. Research should be fostered that will fully characterize the early development of speech perception in the development of the native language. Thus, there are strong needs to:

- Encourage studies to determine when infants begin to learn about specific aspects of native language sound patterns, its prosody including rhythmic and tonal properties, phonetic elements and phonotactic, syllabic and morphologic structure.
- Foster research that can provide critical information about when various general features of language structure, such as phonotactic patterns, are acquired relative to other features, such as prosodic patterns.
- Investigate the range of acceptable or normal individual variability in the acquisition of particular types of language-specific information.
- Pinpoint how the sound structure of the native language interacts with basic perceptual capacities during language acquisition.

Development of Categories

- Investigate the nature of the infant's representation of speech information and how it changes as a result of experience with a native language. This research will include obtaining more information about the type of representational units that are encoded in listening to speech, including the size of the unit; whether they are general prototypes or specific to individual talkers; and whether they are characterized by acoustic or articulatory properties.
- Examine the experiential, biologic and specific linguistic factors that might lead to modifications of representational units.
- Determine whether there are individual differences in the types of representational units used by infants and young children in perceiving and producing speech, the relationship between

perceptual and productive units and the consequences this relationship may have for later language acquisition.

Fluent Speech Perception

- Delineate the basic perceptual capacities of infants and children to discriminate fine differences in speech sounds and obtain information about how such capacities are used in processing fluent speech.

- Determine how and when infants and young children develop the ability to extract information from fluent speech and the nature of the information that is extracted.

- Obtain a better understanding of whether and how infants and young children are able to follow speech in noisy backgrounds, whether there are individual differences in their ability to do so, and how speech information helps children build a lexicon.

- Evaluate the extent to which infants and children are able to cope with the variability in speech. Investigations into the capacity of infants and children to cope with talker, dialect and rate differences in speech are important for understanding normal development and for improving early diagnosis and treatment of speech perception difficulties in young children.

Neural Foundations

- Investigate the relationship of developmental changes in speech processing to changes in the structural and functional development of the nervous system. Studies that relate changes in speech processing to neural changes may yield new insights about the mechanisms responsible for developmental changes.

- Examine the relationship between neural development and individual differences in the timing and acquisition of certain milestones associated with phonologic development.

Characteristics of the Input

Insights about the development of speech perception capacities and their influence on language acquisition should be further studied to provide more precise information about the characteristics of the speech input to which the child is exposed, especially early in life. Research on speech input should include studies to:

- Provide empirical data that could help to settle long standing debates regarding the role of innate and experiential factors in language acquisition. Specific questions to be examined include the extent to which adults enhance phonetic contrasts or engage in phonologic reduction when they address young children.

- Measure the acoustic characteristics of speech directed to infants and the frequency with which such patterns occur. This information should be helpful in understanding the developmental process.

- Improve theoretical models of the ways in which innate and experiential factors interact during the course of language development. Such studies may be helpful in determining the extent to which the acquisition of knowledge about the native language sound system may influence other aspects of speech perception and language development.

Modeling

Information about the general capacities of infants for perceiving speech, coupled with recent findings concerning when infants begin to attend to the structural speech features of their native language, provide an opportunity to develop and test models of phonologic development. Research needs include to:

- Encourage attempts to model the ways in which native-language phonetic and phonologic categories develop from basic speech perception capacities. In particular, modeling approaches may aid in evaluating the extent to which the processes underlying the development of phonologic categories are specific to speech and language, or derived from more general cognitive and perceptual processes.

- Develop theoretical models that attempt to deal with the integration of prosodic and phonetic information in the perception of speech. These models should prove valuable in understanding how fluent speech processing develops.

Multimodal Factors

Parallel investigations of the development of the perception of speech and of native, manually coded languages could offer insights about which processes underlying language acquisition have a modality-specific basis. Research needs include to:

- Compare and contrast the perception of speech and manually coded languages by young children in both language groups.

- Identify the role that specific brain structures play in the acquisition and comprehension of language in the vocal modality versus the manual modality.

Influence of Higher-Order Knowledge

As speech perception capacities of infants and young children develop, there may be important changes in the knowledge sources they bring to extracting information from the speech signal. Viewing the development of speech perception in the context of growth in cognitive and linguistic abilities has important clinical, as well as theoretical, implications. Research is needed to:

- Relate changes in speech processing to achievements in other levels of linguistic knowledge (morphology and syntax). These findings should provide insights about how sources of information interact in speech perception.
- Study the contributions to speech processing provided by information in the visual, haptic and proprioceptive modalities, as well as the deficits that occur when such sources of information are not available. This would help clarify the nature of the mechanisms underlying speech perception and provide useful information regarding its implications for persons who are hearing impaired.
- Investigate the relationship between the development of speech perception and important developmental changes in cognitive abilities. This information will have major clinical and theoretical implications.

Adulthood

Nature of the Speech Signal and its Perception

It is essential to understand the nature of the speech signal, how it is generated, how it is perceived and how the processes of speech perception relate to those of speech production. Research is needed to:

- Gain a better empirical understanding of which properties of speech perception are invariant and which are context-dependent. This information would aid in understanding how listeners perceive speech in less than ideal conditions, in developing automatic speech recognition devices, as well as in improving augmentative and assistive devices, and in determining those cues or properties that are apt to be vulnerable to neurogenic insult.
- Examine the properties of utterances that adult speakers direct to mature learners of a second language, such as speech rate, intonation and phonetic clarification. Compare those with the properties of speech directed to native adult listeners and to young first-language learners.
- Determine the means and extent to which listeners are able to extract

and remember information about talker identity, emotional tone and other nonlinguistic information from the speech signal, and how this information may interact with the processing of linguistic information.

- Investigate the auditory transformations of complex signals to determine how this process structures and ultimately shapes human speech. It is also important to identify the acoustic properties that are information sources about the articulatory gestures used to produce speech.
- Investigate the extent linguistic experience and listener characteristics such as, individual variation and special populations, affect how information is extracted from the speech signal.
- Conduct research to identify the processes listeners use to track speech in the midst of noisy environments, including competing speech signals. This information is important not only to an understanding of normal speech perception but also in identifying deficits in speech, hearing and language, and in developing automatic speech recognition devices.

Influence of Higher-Order Knowledge

It is essential to determine how speech perception relates to higher or more abstract levels of linguistic organization. Critical issues include how speech perception affects or is influenced by word recognition, lexical access, parsing, disambiguation and ultimately sentence and discourse understanding. Research needs to:

- Study the nature of information the listener extracts from the prosody of utterances. This information will help clarify the representation of the input developed by the listener during on-line processing.
- Investigate the role played by factors related to the organization of the lexicon (word frequency and number of phonetically similar items), as they influence speech perception. Information from such studies may have important implications for understanding the nature of deficits in individuals with language impairments.

Modeling

It is critical to develop more comprehensive theoretical models of speech processing. Research efforts should include the following:

- Develop models that describe how listeners extract linguistic meaning from spoken input. Such models have importance for research on natural language understanding, automatic speech recognition devices and the development of better clinical tools for identifying and treating language and hearing disorders.

- Provide complete details on competing models of speech perception so that they can be empirically tested. Empirical testing would enable investigators to converge on the correct account of speech perception mechanisms and provide a theoretical framework to pose research questions, to establish research strategies and priorities, and to develop efficacious assessment and treatment strategies.
- Model how the acoustic signal is transformed by peripheral and central auditory processing mechanisms, which will be valuable in constructing theories of speech perception.
- Encourage cross-species studies that model the way complex, biologically relevant signals are perceived.
- Develop computer simulations that attempt to model recognition of fluent speech as a useful way of evaluating the feasibility and psychological plausibility of speech processing models.

Cross-Language and Second-Language Learning

Studies that compare the perception of individuals who speak different languages, as well as studies that compare native and nonnative speakers of English, afford unique opportunities to understand the organization and development of perceptual processes in response to experience with a specific language. Investigations are needed to:

- Pinpoint differences in categorical representations of native and nonnative listeners and elucidate the extent to which categorical representations may change upon exposure to a second dialect or language.
- Test for differences in syllable processing strategies that might arise from language-specific differences in phonotactic constraints (rules that govern sound combinations) or syllable organization.
- Determine differences in degree of attention to various aspects of the speech signal that might arise from language-specific differences in phonetic and prosodic patterns.
- Extend previous psycholinguistic research that has concentrated on the role of lexical familiarity to the study of perceptual adjustments during second-language learning.

- Quantify the role of age in second-language learning or duration of use of English as a second language on English language comprehension, in both ideal and non-ideal listening conditions and with single and multiple talkers.

- Foster the development of multisite national and international research collaborations and networks that are needed for high quality cross-language and cross-dialect studies.

Fluent Speech Processing

- Investigate the processes involved in the perception of fluent speech and the sequencing and interaction of those processes in on-line perception.

Neural Foundations

Studies of the neural underpinnings of speech perception, including the processes involved in accommodation to variation in speech properties and the influence of higher-order knowledge, are essential for the development of theoretical models. Such models of the underlying mechanisms will yield better insights into the effects of brain damage and neurogenic disorders on speech perception. Research targets include:

- Encourage the investigation of brain mechanisms involved during on-line speech perception.

- Foster studies that will provide a broader picture of the full range of speech capacities in brain-damaged, neurogenic-impaired and other special populations, such as persons who are bilingual or congenitally deaf or blind.

- Develop a fuller understanding of the organization of the auditory pathways and central brain structures and functions that are relevant to speech processing.

Aging

The increase in auditory and nonauditory sensory losses, as well as the increased incidence of central deficits in processing that occur with normal aging, is likely to affect speech perception and communication. There has been relatively little research, however, on speech perception in the elderly. It is important that a deeper understanding be gained about the effects of aging on speech processing. Research opportunities include the need to:

- Conduct studies investigating speech perception skills in the normal elderly and in the elderly following gradual or sudden hearing loss or brain damage.

- Develop standardized assessment protocols that quantify speech perception capabilities in the elderly, based on recent experimental findings, especially for detecting perceptual difficulties in the elderly experiencing cognitive deficits (multi-infarct dementia and Alzheimer's disease) and those experiencing multisensory losses (hearing and vision).

- Determine whether changes in speech perception normally occur with aging and, if they do, assess the extent to which they affect language comprehension skills.

Disorders Affecting Speech Perception

Peripheral Auditory Disorders

Studies are needed to depict how different aspects of the acoustic speech signal are affected by peripheral hearing loss, and to determine how hearing loss influences speech perception and its contribution to communicative development. Research should strive to:

- Investigate the perceptual consequences associated with conductive hearing losses.
- Conduct developmental studies of speech perception in children with varying degrees of sensorineural hearing impairment.
- Evaluate the influence of alternative sensory devices, such as tactile aids, hearing aids and cochlear implants on speech perception in hearing-impaired populations.
- Investigate the influence of different speech processing strategies on speech perception involving the use of various assistive sensory devices.
- Conduct treatment efficacy studies evaluating aural rehabilitation techniques used to improve speech perception and production in individuals with hearing impairments.
- Improve the assessment of speech perception skills in people with hearing impairments based on the study of normal speech perception.
- Encourage studies designed to assess speech perception using tasks which do not require higher-order language skills.
- Explore the perceptual consequences of auditory only, visual only and combinations of auditory-visual presentations to individuals with hearing impairments.
- Study the psychoacoustic characteristics of persons with hearing impairment and how these characteristics relate to speech perception.
- Conduct studies exploring the relationships of speech production and perception in persons who are hearing-impaired.

- Promote studies examining the wide range of performance variability in individuals who are hearing impaired to elucidate why some achieve higher performance than others on measures of speech perception and production.

Central Auditory System Disorders

Additional knowledge is also needed regarding the effects of various central auditory disorders on the ability to perceive speech. Research should be fostered to:

- Study the speech perception and production skills of children with central auditory processing disorders.
- Examine the consequences of neurogenic disorders and insults, such as aphasia, apraxia, brain injury, Parkinson's disease, amyotrophic lateral sclerosis, on speech production and perception. Investigations of these disorders may provide particularly important insights regarding the relationship between speech production and perception and their breakdown.

Phonological Disorders

Additional information is needed on the role of perception in productive phonological disorders. Such advances will contribute to the differential diagnosis of these disorders and will influence the nature and course of intervention. Research should include studies to:

- Isolate the basic perceptual abilities of young children and identify how the abilities change with normal development. These data will provide a baseline for comparison with the perceptual skills of children who are affected by phonological disorders.
- Establish parallels between the development of perceptual categories and the emergence of the productive phonology in children, especially with respect to identifying the basic units of phonological systems in the perception and production of speech.
- Determine the nature, degree and extent of perceptual breakdown in speakers with productive phonological disorders.
- Develop and evaluate reliable and valid methods of assessing perceptual deficits in speakers with phonological disorders.
- Determine the efficacy of the perceptually based, as opposed to production-based, treatment of phonological disorders.
- Isolate the contribution of speech perception to disorders of phonology and determine the role of perception in treatment.

General Topics

There are a number of related research issues on the perceptual skills of speakers with various characteristics. Research should:

- Continue to investigate the relationship between reading proficiency and speech perception capabilities in good and poor readers. Contrast the performance of good and poor readers on tasks manipulating input modality (visual versus auditory versus multimodal) and cognitive demands (memory load) as well as linguistic factors (lexical familiarity or phonological structure).

- Explore the speech perception capabilities and limitations of individuals with autism.

- Initiate studies evaluating speech perception performance and difficulties in other populations with communication disorders (developmental language impairment) or conditions which place individuals at risk for communication disorders (substance abuse, HIV infection or lead poisoning) to assess the perceptual contributions to communication difficulties.

- Examine the relationship between cognition capabilities and speech perception in individuals with mental retardation syndromes that are nonspecific for communication deficits, such as Down syndrome or Williams syndrome.

- Investigate the effects of traumatic brain injury on speech perception and its relation to speech production and language in affected individuals.

Cross Cutting Topics

Research Methodologies

Conceptual Underpinnings

Some general research opportunities in this area are listed below:

- Encourage research designs that examine the contributions and interactions among biological, experiential and social factors in all areas of speech production and perception development.

- Conduct research on speech perception and speech production within a developmental, lifespan perspective, using longitudinal as well as cross-sectional and single subject designs, and retrospective as well as prospective approaches.

- Base speech perception and production research on clear tests of hypotheses derived from theoretical models that generate testable hypotheses.

- Encourage increased application of molecular genetic and biologic techniques to the study of speech and speech disorders.

- Conduct genetic research on speech disorders, including description of behavioral phenotypes and family linkage.

Measurement Issues

Research is needed to develop standardized, reliable and valid methods to measure relevant variables in speech research. Examples of research needs include, but are not limited to, the following:

- Develop standardized acoustic, aerodynamic and kinematic measurements of speech production.

- Develop culturally sensitive assessment instruments for studying multilingual and multidialectal and non-native language populations.

- Develop protocols based on current scientific knowledge of normal populations and that include recognized clinical criteria for disorders and for relevant subclinical or variant conditions.

- Develop new methods and tools for studying on-line perception of fluent speech and for studying the range of variability in speech production and perception.

- Encourage the development, refinement and use of new and emerging technologies in speech research and clinical applications. These include, but are not limited to, brain imaging techniques, genetic studies, neurochemical approaches, measures of speech articulatory events, computer modeling and simulations, automatic speech recognition and synthesis.

- Develop techniques for collecting reliable and valid data on the perception and production capacities of the toddler, preschooler and the young school-aged child.

Research Approaches and Designs

Descriptive Studies

Descriptive studies are used to provide data on incidence, prevalence, and sociodemographic characteristics. These kinds of data are typically collected in population-based epidemiologic surveys. Studies are needed to:

- Determine the incidence, prevalence and occurrence of disorders of speech perception and production, including potential racial, ethnic and gender differences.

- Examine the range of normal variability in speech perception and production, including multicultural and gender differences.

- Characterize the relationship between speech disorders and broader sociocultural factors that may be affected by the disorders, such as academic performance, school drop-out rates, employability, continuing education and training in changing job markets.

Analytic Epidemiology

Analytic epidemiologic studies are used to identify independent risk factors for the development of speech disorders. These studies can be population-based or clinic-based. A critical condition of analytic epidemiology is the statistical quantification of the amount of risk associated with a particular factor. Such information can be important in assessing potential causes, identifying concurrent conditions and developing appropriate experimental treatments. Studies are needed to:

- Conduct case-control (retrospective) and cohort (prospective) studies to: identify risk and protective factors (including genetic factors) for disorders of speech perception and production, quantify risk and examine concurrent conditions. Studies may include individuals with multiple anomalies and investigations of early indicators.

- Apply current techniques of molecular genetics and familial linkage research to elucidate the hereditary basis of various disorders of speech production and perception. Special concern should be paid to bioethical considerations in this and other approaches characterizing biological markers and risk factors in speech disorders.

Experimental Research Strategies

Experimental strategies for testing treatment efficacy need to follow an organized and systematic research program in which treatment research progresses from hypothesis development, through methods development, to randomized controlled clinical trials. Investigations are needed to:

- Establish a program of developmentally appropriate, controlled clinical trial research.

- Extend treatment studies to include follow-up evaluations on retention, comparisons of long-term versus intermittent treatment, incidence of relapse and age of intervention.

Other Research Designs

Studies that employ other methodologies and designs are extremely important in indicating potential risk and protective factors for disorders of speech perception and production. Such studies should:

- Support longitudinal studies as a means of providing in-depth developmental data on normal and disordered development.
- Encourage and support studies comparing various factors in differing communities and cultures in order to describe variations in communication behaviors in various ethnic and racial groups.

Multicultural Issues

Important areas of research that are uniquely applicable to the multicultural community include: the effects of second language or dialect acquisition on speech perception and production; the effects of multiple transient ischemic attacks and strokes on the development of speech perception and production in individuals with sickle cell disease; the effects of otitis media on speech perception and production in specific populations; as well as the management of cleft lip and palate in populations such as African Americans who are prone to formation of keloids. Research is also needed to explore the influence of cultural variables on clinical management, the most effective language for treatment in the instance of bilingual and bidialectal speakers and other issues pertaining to service delivery, such as the development of linguistically and culturally appropriate assessments and treatments. Because of the variability in subjects across the population and within the multicultural communities, it is recognized that research on multicultural issues may entail the use of innovative paradigms such as single subject studies and comparing multiple factors in subcultures.

Normative Data

Research is needed to:

- Develop communication ability norms in the areas of speech perception and speech production. Available normative data should reflect the cultural and linguistic diversity of the United States population.
- Develop cross-cultural and cross-ethnic investigations of acoustic parameters of speech. Also include studies of the anatomic and physiologic bases of diversity in speech production and speech perception across subgroups of the multicultural population.

Incidence, Prevalence, Risk Factors and Utilization of Rehabilitation Services

Research effort is needed to:

- Conduct epidemiologic surveys to determine the incidence and prevalence of communication disorders (including auditory disorders and disorders resulting from laryngeal cancer, cleft lip and cleft palate) for populations from the multicultural community.

- Conduct epidemiologic studies to uncover the effects of important independent variables such as, poverty and race, on the incidence and prevalence of various communication disorders.
- Delineate the specific health and environmental risk factors associated with various categories of communication impairment among people from different multicultural communities.
- Conduct rehabilitation needs assessments for populations from the multicultural community.
- Determine the factors that influence access to and utilization of rehabilitation services for populations from the multicultural community.

Research Topics Unique to the Area of Multiculturalism

Research is needed to:

- Determine the effects of sickle cell disease and other disorders associated with specific populations on the communication process.
- Investigate the influence of culture and cognitive style on treatment effectiveness and efficacy.
- Investigate treatment efficacy and clinical practices that are implemented with bilingual and bidialectal populations.
- Investigate second language or second dialect development in multilingual and multidialectal speakers.
- Investigate the influence of second language and dialect learning on the development of various aspects of normal speech and communication, such as fluency.
- Investigate the influence of multilingualism and multidialectalism on the development of speech in children with communication disorders.
- Investigate the influence of multilingualism and multidialectalism on treatment for speech impairments in adult populations.
- Conduct cross-cultural research to determine specific cultural perceptions regarding factors that constitute impaired speech production and impaired speech perception.
- Develop culturally and linguistically appropriate assessment procedures to facilitate the identification of language impairment (versus language difference) among individuals from

culturally and linguistically diverse populations.

- Develop culturally and linguistically appropriate treatment paradigms and models of service delivery for individuals from the multicultural population.

- Develop procedures for determining the most effective language of treatment for multilingual and multidialectal speakers.

- Investigate the social implications of nonstandard English language and dialect as a function of the educational, vocational and social contextual setting and listener variables.

LANGUAGE AND LANGUAGE IMPAIRMENTS

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LANGUAGE AND LANGUAGE IMPAIRMENTS

Overview

Language is the expression of human communication through which knowledge, belief and behavior can be experienced, explained and shared. The ability to manipulate language to satisfy needs and desires and to express thoughts, observations and values is an important human pursuit that directly influences the quality of life for any individual.

The broad goals of research on language are to understand the nature of normal language function, including the underlying bases and mechanisms involved. One goal of this work is to build the foundation necessary to develop and evaluate intervention and rehabilitation strategies to improve and enhance the communication process for individuals with language disorders. The understanding of normal language (whether spoken, signed or written) provides a basis for comparison in investigations of language disorders. It is critical to understand how language is produced and understood, what its biological and neural substrates and organizing principles are, how it is learned by children and how it is processed.

For an adequate understanding of language functioning in children and adults, research efforts must include all of the diverse groups that make up contemporary United States society. These populations include racial and ethnic minority groups and groups categorized in terms of gender, age, geographic region and social and economic status.

In the United States, there may be as many as one half million persons who were born deaf or who lost their hearing before they acquired spoken language. In the world at large the number may approach 10 million. A large proportion of these individuals use a form of signed language as their primary mode of communication. Some use spoken English exclusively. Many use both. Research and services related to deafness must be concerned with the impairment of auditory language and with the status of and access to signed or spoken languages which are perceived visually.

There exists another group of at least one million people whose hearing impairment is less severe but was acquired during childhood. Most of these individuals use spoken language as their primary mode of communication, although some also use a signed language. Despite the substantial benefit of auditory input to such people, their language acquisition is often characterized by difficulties not faced by normal hearing people.

Individuals with normal hearing, as well as those with a hearing impairment, may exhibit a disorder of language, that is, a deficit of language comprehension, production or use sufficient to impair interpersonal communication. In young children, these disorders frequently involve difficulty in the acquisition of the ambient spoken or signed language and may also lead to impairment in reading and writing. In adults and older children, impaired persons include aphasic individuals who have lost their previous levels of language competence as a result of brain injury.

Language impairments impede economic self-sufficiency, academic performance and employment opportunities. It is estimated that between six and eight million individuals in the United States have some form of language impairment. In addition to loss of livelihood, these disorders impose social isolation and personal suffering on the affected individuals and place an enormous emotional and economic burden on their families and on society as a whole. These disorders have a life-long impact on the ability of those affected to make their way or even to survive in our technologically advanced society.

Disorders of language affect children and adults differently. For the child who does not use language normally from birth or who acquires the impairment in childhood, the disorder occurs in the context of a language system that is not fully developed or acquired. In contrast, damage to the language apparatus in adults disrupts a system that is less malleable in the face of neural damage. Adults with aphasia commonly have highly selective deficits and more highly developed compensatory mechanisms. Neurologic, physiologic and metabolic differences between children and adults provide particular problems and challenges to the study of language disorders in these populations. As a result, while the broad goals of research on language disorders are similar for children and adults, the research agendas for these two groups are considered separately.

Recent Accomplishments

Multicultural Issues

The majority of children from all cultures acquire language with little difficulty, including those who are reared in multicultural environments. However, the assessment of disorders within multicultural groups can be complicated by a variety of factors. For example, individuals who are members of multicultural populations such as African-, Asian- and Hispanic-Americans may be incorrectly identified as language impaired due to the use of culturally inappropriate language assessment instruments. On the other hand, such groups are more likely to live in conditions of poverty, which give rise to various health and social conditions that are linked to increased risk of communication disorders.

There are likely to be pertinent differences in prevalence, causes and manifestations of language disorders among diverse cultural populations. For example, sickle cell anemia, a condition associated with an increased prevalence of sensorineural hearing loss and neurological impairment, is estimated to occur in one in every 500 African-American children. To the extent that these complications directly influence language learning, such children are at considerable risk. Current data also show a very high prevalence of chronic middle ear disease among Pacific Rim, Alaskan Native and Native American populations. The prevalence of hypertension and diabetes, two of the primary risk factors for stroke, may be higher among low socioeconomic groups. Thus, there is likely to be an increased occurrence of aphasia in these groups.

Language disorders have been found to occur in children with elevated blood lead levels. The highest blood lead levels have been found in children living in low-income households within the inner cities of large urban areas.

Language Among Deaf Children and Adults

Language acquisition takes place naturally for most children; those who have normal hearing and those who are deaf with signing deaf parents. Many deaf children use a natural sign language, American Sign Language (ASL), which shares an underlying organization with spoken language. Recent electrophysiological findings show that, in spite of the very different input/output systems employed, the same areas in the left hemisphere of the brain are involved in language tasks in native signers and speakers of English. However, despite the ease with which they acquire ASL, many deaf children of deaf parents have inordinate difficulty learning to read and write.

Studies of the acquisition of ASL suggest that signers acquiring the language at a later age demonstrate grammatical deviations from more standard ASL. These deviations persist even four or five decades after acquisition has taken place. This finding suggests the existence of critical periods for acquiring signed language that parallel those documented for spoken language.

Studies of deaf children of hearing or oral deaf parents indicate that, with intensive oral training, their acquisition of spoken language and reading tends to be superior to that of deaf children with equivalent levels of hearing impairment who do not have such training. However, deaf children of hearing or oral deaf parents often display substantial delays learning to read and write.

The dominant pedagogical methodology employed currently in the United States in teaching language to deaf children involves the exposure to artificial signing systems, which are intended to represent and model English and to promote the natural acquisition of English grammar. Recent research suggests that deaf children of hearing parents, when exposed only to artificial signing systems, develop some idiosyncratic grammatical patterns that may not reflect the structure of English or of ASL.

Another methodology currently employed emphasizes the development of spoken language exclusively. Some deaf children exposed to this method throughout their educational program achieve English language competence without the knowledge of sign language.

Cued Speech, a system of communication which uses simple hand cues in conjunction with the natural mouth movements of speech, emphasizes the natural development of spoken language. Many deaf people exposed to this system throughout their educational history achieve English language competence.

Just as speech is one of the basic building blocks of language for hearing people, signing is one of the basic building blocks of language for some deaf people. Thus, the study of sign language perception is as critical to an understanding of the language of many deaf people as the study of speech perception is to understanding the language of hearing people and deaf people who use auditory and/or visual means for perceiving spoken language. Such studies will provide insight into the nature of language processing in deaf people and will lay the foundation for understanding disorders of spoken language that may occur in certain deaf persons. Comparisons of the processes of spoken language perception and signed language perception in normal and language-disordered hearing and deaf individuals provide a unique means of determining those aspects of language that are independent of the mode (signed or spoken) of communication. Such findings may be used to develop appropriate rehabilitation strategies, depending upon the nature of the language deficit.

Studies of the acquisition of sign suggest that infants are very good at relating information in one sensory modality with information in another. Deaf infants learning a signed language rely on movement of the hands and arms, as well as processing by the eye. New technology for three-dimensional motion analysis has been developed for the study of signed language perception, and investigations are now under way that will allow one to separate constraints imposed by the transmission modality from more centrally determined factors in the perception of the basic building blocks of language.

Central to the understanding of disorders of spoken and signed language perception in the hearing impaired is an understanding of normal processes. Research advances in the past 10 years have focused primarily on spoken language perception in normal persons and while many advances have been made, scientists are only beginning to understand fully the nature of the spoken and signed language perception process.

For most people, spoken or signed language, or a combination of the two, are the ways to express thoughts and ideas and to communicate with each other. How spoken or signed language perception interacts with syntactic and semantic knowledge in language comprehension is still not understood. The increased availability of precise instrumentation techniques and use of more sophisticated research methods promise to provide a richer understanding of the nature of spoken and signed language perception. Largely through the efforts and cooperation of many different kinds of scientists (speech, language and hearing scientists, engineers, linguists and psychologists) research on this topic is beginning to contribute a multi- and inter-disciplinary perspective to this complex but critical problem.

Language and Language Disorders in Children

The study of language acquisition in normally developing hearing children has provided an important foundation for research with language-disordered children. Findings on both the course and underlying bases of language development have been reported. It is clear from this work that infants have available at birth, or quickly develop, many of the perceptual, cross-modal (auditory-visual) and conceptual abilities necessary to learn language. Differences among individual children's language learning patterns have been identified, as well as differences in learning according to the type of language being acquired (e.g., morphologically rich like Italian vs. word-order-dominant like English). Although much research remains to be done, the existing knowledge has greatly facilitated the study of language impairments.

Language disorders among hearing children can be discussed in terms of whether the language difficulties exist in isolation or in association with other problems and whether the factors interfering with language were present from birth or appeared subsequently.

Many children with isolated language problems that appear to be present from birth are given the clinical label of specifically language impaired (SLI). These children show normal hearing, age-appropriate scores on standardized tests of nonverbal intelligence and no overt evidence of neurological damage. Although U.S. prevalence data need to be more firmly established, it is estimated that approximately five percent of preschool children fall into this clinical category.

Although SLI children do not show signs of frank neurological impairment, neuropsychological studies have revealed that these children perform poorly on perceptual and memory tasks, especially those involving the processing of rapid acoustic changes. These findings cast doubt on the presumed isolation of the language difficulties.

Investigations of the language skills of SLI children have focused on syntax, morphology, phonology and semantic relations. These studies have revealed significant limitations in each of these areas. Although each area is acquired in a manner approximating normal development (albeit more slowly), the language profiles across areas often do not match those of younger, normally developing children in that certain areas (for example, morphology) may show an especially serious deficit. Because studies have focused exclusively on SLI children acquiring English, it is not known whether the observed profiles reflect general difficulties with particular grammatical functions or are influenced by the manner in which these properties are marked in English. Several retrospective, follow-up studies of SLI children have suggested that residual problems with language and language-related learning problems may be seen through adolescence and into adulthood.

Research in recent years has begun to address the problem of inadequate subject description of SLI children. This work has provided a protocol for selecting prototypic groups of SLI children. Projects devoted to distinguishing among subgroups of SLI children are now under way.

Efforts aimed at the early identification of SLI children are also in progress. It appears that children's expressive vocabulary size, vocabulary comprehension and use of symbolic gestures assist in determining whether late-talking children are at risk for language impairment.

New technologies such as magnetic resonance imaging (MRI) and event related potentials are beginning to be applied to SLI children. Research to date suggests that SLI children show an atypical left-right hemispheric configuration. Genetic studies of SLI children have also been undertaken. The preliminary findings from these studies suggest that SLI children are more likely than normally developing children to have other members of the family with present or resolved language difficulties.

Research on the phonologic, morphologic and syntactic features of language that are difficult for SLI children, as well as on the perceptual and motor abilities of these children, has continued. In addition, the lexical (vocabulary) and pragmatic (communicative-conversational) abilities of SLI children have received investigative attention.

Prospective longitudinal research on SLI children has begun. The results of these studies indicate long-term deficits in these children. Evidence is accumulating that young SLI children are clearly at risk for later deficits in reading and that SLI and reading-disabled children represent overlapping populations.

For many children with language disorders, limitations in other areas are also evident. Some of these multiple disabilities result from maternal substance abuse in pregnancy, fetal and infant malnutrition, lead poisoning, congenital AIDS and prematurity in the children of adolescent mothers without prenatal care.

In terms of prevalence, mental retardation is the most common disorder associated with inadequate language development. Recent research shows that children with mental retardation can have a variety of language disorders and that mental retardation often offers an inadequate explanation for communication problems in these children. A common genetic form of mental retardation, Down syndrome, has been shown to be associated with greater impairment of expressive than receptive language. Fragile-X, probably the most common single cause of genetic mental retardation in males, affects language meaning and use more than it does the acquisition of phonology and syntax.

Autistic children constitute another group in whom language is but one area of deficiency. Inadequate communication skills are hallmarks and the most common presenting symptoms of autism, but nonlinguistic deficits make separate contributions to its symptomatology. Nonetheless, it is now clear that, while autism is associated with mental retardation in some children, mental retardation is not a defining feature of the disorder.

Other conditions that can complicate the normal acquisition of language relate to the availability of an adequate listening environment early in life. This need is illustrated by three findings. First, there are some data to suggest that chronic otitis media in the developing infant, when accompanied by a mild and intermittent hearing loss, may be predictive of later language impairment. Second, there is evidence that early amplification and auditory training can significantly affect the deaf child's acquisition of spoken language. Third, there is evidence that normal infants and children need a more favorable signal relative to the background noise to perform at the same level as the adult in spoken language perception tasks.

Some language disorders in children are acquired through infections, tumors, stroke or trauma. Strokes in children are estimated to have an annual incidence of 2.52 per 100,000 children. Other causes, such as head trauma are estimated to be as high as 200 per 100,000 per year.

Advances have been made in specifying the relationship among acquired language deficits and the focality or diffuseness of central nervous system (CNS) involvement, lesion laterality and age at lesion onset. Children with focal, unilateral lesions, such as those sustained following vascular episodes, generally have been found to have better long-term language development and recovery than children with lesions involving more diffuse brain structures, such as CNS tumors treated by whole head radiation and chemotherapy, severe closed head injury or epileptic aphasia. Both fluent and nonfluent aphasias may occur in children with acquired brain lesions, and a variety of syntactic and lexical comprehension and production deficits have been described following left hemisphere lesions. Delays in lexical development and in the development of syntactic structures have been documented following early lesions of either the left or right hemisphere. Attempts to relate language sequelae to lesion location within a hemisphere have been equivocal. Prognosis related to age at lesion onset is controversial and confounded by factors such as the diffuse nature of the lesion, concomitant seizure disorders and questionable premorbid status. Studies using electrophysiologic and neuroimaging techniques are beginning to address the nature of hemispheric reorganization following acquired language loss in children.

Language and Language Disorders in Adults

Current best estimates place at nearly one million the number of adults in the United States with acquired disorders of language due to stroke or traumatic brain injury. Additionally, a large proportion of the estimated two million citizens with progressive dementing disease have significant language impairment. Their disabilities range from partial impairment that affects primarily one or two input or output channels to near total and permanent loss of comprehension and production of speech. While many are rendered totally dependent, there is a wide range of possibilities for rehabilitation of communicative power and, in some cases, the return of economic self-sufficiency.

Impairments in the comprehension, production or use of language by adults are encountered in a variety of clinical settings. Acquired language disorders are frequently observed, for example, in patients with stroke, head injury, dementia, brain tumors and CNS infections (including AIDS). Language disorders are also found in adults who have failed to develop normal language because of childhood autism, hearing impairment or other congenital or acquired disorders of brain development. Although deficits of spoken language frequently affect all language modalities, that is, reading, writing and the signed languages of deaf people, dissociations in performance as a function of language modality do occur. Thus, for example, patients with acquired disorders of reading or writing may be essentially normal in spoken language. Lastly, disorders of language, or communication more generally, may be encountered in patients with dysfunction of the non-dominant hemisphere. Specific impairments in the interpretation of communicative intent, as well as in the ability to appreciate several alternate meanings of a word, have been demonstrated after stroke involving the right hemisphere.

Research on the ways in which adult language can break down following brain injury necessarily builds upon an understanding of how language comprehension and production are accomplished by normal people. The development of experimental techniques for analyzing language functions and for investigating the neuroanatomic representation of those functions in the brain constitutes an important component of current efforts in this area.

The understanding of the anatomic and physiologic bases of normal and disordered adult language has, in recent times, been facilitated by the application of a variety of experimental techniques. Contemporary computed tomography (CT) and magnetic resonance imaging (MRI) scans offer precise information about lesion size and location heretofore available only at autopsy. These data have, for example, contributed to a better understanding of the anatomic basis of speech initiation and production. Imaging of brain metabolism and blood flow using positron emission tomography (PET), as well as single photon emission computed tomography (SPECT), has contributed substantially to the understanding of the functional anatomy of the language system in normal subjects as well as in patients with brain dysfunction. These studies of dynamic brain activity have also led to a greater appreciation of the important interactions between language and other cognitive operations. Electro-cortical stimulation techniques have also contributed to the understanding of the functional anatomy of the language system. The analysis of the consequences of transient electrically induced cerebral "lesions" has facilitated the identification of discrete language mechanisms and has engendered better understanding of the individual variability in the cortical representation of language functions. Finally, additional electrophysiologic techniques, such as event-related potentials (ERP) as well as advances in the mathematical modeling and signal processing of electroencephalographic data, have assisted in the understanding of the temporal course and anatomic representation of language processes.

The theories and methods of modern cognitive science have brought about important refinements in understanding the cognitive processes that normally underlie language functions. For example, chronometric investigations of the course of auditory language comprehension have highlighted the complexity of the processes required to integrate aspects of word meanings with elements of sentence structure. These new insights have motivated the development of tests that allow the attribution of specific aphasic symptoms to failure within identifiable components of the language system. These advances have, in turn, provided the groundwork for the development of new approaches to diagnosis and rehabilitation of aphasia and acquired dyslexia.

Several recent findings await further study and fuller exploration. For example, common mechanisms underlying spoken language and the signed language of deaf people have been dramatized by the identification of striking parallels in the effects of brain injury on these two modes of communication. Artificial intelligence computer models of language have offered insights into the processes mediating language; additionally, disruptions or "lesions" of these models permit the simulation of symptoms and promise to provide a means for the testing of hypotheses concerning the basis of particular language deficits. Cross-language comparisons of sentence production and sentence comprehension disorders have begun to distinguish between symptoms that are universal in their form of presentation and those that are specific to the structure of particular languages.

Recent advances in the remediation of language disorders include the demonstration that some profoundly aphasic patients can learn a computerized system for exchanging information by manipulating visual symbols. In fact, computer-assisted assessment and instruction are active areas of current research interest and promise to allow the testing of previously untapped cognitive capacities in severely impaired patients. Explorations in the pharmacologic treatment for aphasic symptoms have shown promise for the relief of selective disorders, such as impairments of speech initiation, through the use of the dopamine agonist, bromocriptine.

Several more traditional treatment programs have been shown to be efficacious with specific types of aphasic patients. These include language oriented and language stimulation treatment techniques as well as interventions designed to bring about well-defined outcomes such as the elimination of the perseverative intrusions of earlier utterances. Additional intervention strategies currently being tested include treatment protocols targeted directly at theoretically defined language components that are found to be impaired. A limited number of such studies conducted to date have demonstrated measurable improvement among individual aphasic patients many years following onset of their aphasia. These studies represent a direct application of results gathered previously in cognitive and linguistic studies of aphasia.

Recent accomplishments in the area of adult language and its disorders have built upon advances in neuroanatomic and neurophysiologic diagnostic procedures, as well as on developments in linguistic theory and cognitive science. Assessment and rehabilitation of these deficits continue to rely on the clinical expertise of speech-language pathologists with new participation from the fields of neuropsychology, pharmacology and computer science. This diversity reflects the complex and multifaceted nature of adult language disorders and provides a broad base upon which to develop a research agenda for the future.

Program Goals

A coherent program that addresses the topic of language and its various impairments must build upon previous accomplishments. At the same time, such efforts should fully exploit emerging technological advances and should accommodate widespread social changes that are likely to affect the acquisition of language and its use.

Several general themes are evident in the research priorities that can be developed to address specific impairments of language. One compelling requirement for improving our understanding of and responses to language impairments is comprehensive data relevant to the incidence and prevalence of these impairments in the population. Systematic study of the epidemiology of these disorders, together with detailed information about the medical, social and cultural conditions with which they occur, would provide a foundation for approaching the important program goal of prevention of language impairments. A second basic requirement that is crucial to understanding any language impairment is detailed information about how language (in all of its auditory and visual manifestations) is acquired and used by normal individuals. The development of theoretically based, methodologically rigorous and culturally unbiased test instruments, as well as the gathering of comprehensive normative data using such instruments, is central to this effort. In light of the growing role that diverse racial, ethnic and social groups play in society, it is essential that these populations be properly represented in the subject pools for studies of normal language processes.

Many language impairments occur because of brain injury or because the nervous system does not develop normally. A better understanding of the mechanisms by which the human brain acquires and processes language would greatly aid in the prevention and rehabilitation of many types of language impairments. Consequently, the exploration of newly emerging technologies for relating language functions to brain regions is a priority.

In addition to these general program goals, areas of specific concern can be enumerated.

- Research on the language of deaf people requires particular attention to the specific needs of deaf children acquiring language in different learning environments. The effects on spoken and signed language development of early exposure to spoken English, signed English and ASL needs to be determined. The effects of differing levels of auditory information on spoken language development need to be rigorously assessed, particularly with regard to improvements provided by new assistive devices. Special attention should be directed to the factors that relate to the acquisition of literacy by deaf people, with the goal of developing methods for enhancing the acquisition of written language by improving English language instruction and by exploiting the child's existing language capacity.

- Basic research on the structural characteristics of signed languages is needed to enhance comparison with information about spoken languages. In addition, continued investigation of differences and similarities in the way the brain processes spoken and signed languages is needed.

- Research on how signed languages are perceived and learned would contribute important information on the development of methods for teaching signed languages to deaf and hearing individuals.

- Studies of children with language disorders should be devoted to several types of issues. Information is still needed on the linguistic, motor, neurogenic and cognitive bases of language disorders in children.

- Valid and reliable language assessment tools are still needed. There is an especially critical lack of assessment instruments for children from multicultural populations.

- The long-term consequences of language impairment warrant further study. Although it is well established that language disordered children are at risk for later academic, social and vocational difficulties, the nature and degree of these relationships must be determined with greater precision.

- There is a pressing need for research on language intervention and treatment efficacy with language-disordered children. Although studies to date indicate that treatment is effective, many specific questions (for example, the criteria used to match particular children with particular treatment procedures) are unanswered.

- A fuller understanding is needed of how language in all of its many aspects is related to the anatomy and physiology of the brain. Relevant data may come from lesion studies seeking to map specific language capacities to brain regions and assessments of the functional anatomy of language in normal and brain-injured subjects using current imaging and electrophysiologic techniques.

- The identification of the component processes underlying normal language remains a high priority. Investigations motivated by current theories of language processing of normal subjects employing spoken, written and signed languages, as well as detailed studies of patients with language deficits, will be relevant.

- Improved understanding of the structure of normal language, as well as technological advances in computer applications, provide a basis for the development of innovative means for evaluating the language-impaired individual's symptoms and for addressing the deficits that are uncovered. Critical to this endeavor will be the development of experimental designs to evaluate the utility of the assessment instruments and the effectiveness of new and existing treatments.

- Finally, a rich source of data about language organization and potential breakdown is available from the comparison of the various manifestations of language impairment. Comparative studies can reveal mechanisms common to different causes and should provide a rational basis for diagnosis and treatment.

Research Opportunities

Multicultural Issues

Although United States society is increasingly multicultural, little research has focused on the implications of social and cultural differences for language and its impairments. Future investigations should:

- Include normative studies for different languages or social dialects which focus on the acquisition and use of phonological and grammatical forms as well as content and pragmatics. Investigations of the simultaneous or consecutive acquisition of two or more linguistic systems are also necessary. Such research can include investigations of "critical periods" for dual language learning and code switching.

- Obtain basic epidemiologic information on the incidence and prevalence of and risk factors for speech, language and hearing disorders within African-American, Hispanic, Asian/Pacific Islander and Native American populations, as available data may not be generalizable across these groups.
- Explore factors that might impede the efficacy of treatment, such as differences in cognitive or learning styles and cultural systems of belief.
- Develop means of differentiating between language differences and disorders across cultural groups.
- Investigate the incidence and prevalence and risk factors for adult neurogenic impairment among culturally diverse and bilingual populations.

Language and Deaf People

The research needs for language and deaf people fall into three broad areas encompassing study of language development in children, literacy in deaf children and adults and basic research on sign language structure and function.

Language Development in Deaf Children

There is some evidence that, if other variables are held constant, deaf children of deaf parents may tend to outperform other deaf children on a variety of academic and psychosocial measures. A full explanation of this phenomenon is lacking and requires further study.

Studies are needed of normal patterns for acquisition of ASL and their relation to cognitive and psychosocial development among deaf children of deaf parents. In addition, to understand normal patterns of such development, it is necessary to pursue parallel studies of disordered courses of development of signed language in the same group.

Because deaf children of deaf parents constitute only a small percentage of the population of deaf children (between five and 10 percent of the total), it is imperative that a better understanding of typical patterns of language development of deaf children of hearing parents be pursued.

Within this area, new studies are needed to:

- Identify and describe patterns of acquisition of ASL, particularly when access to a first natural language is delayed or incomplete.
- Identify and describe patterns of language acquisition of children exposed primarily to systems or

styles of signing in which the intention is to model or support English speech.

- Identify and describe patterns of language acquisition among children exposed primarily to oral language.

- Identify and describe patterns of language acquisition of children primarily exposed to spoken English through Cued Speech.

- Identify and describe patterns of related cognitive, psychological and academic deficits accompanying delayed language acquisition.

- Study the nature and value of language models provided by hearing adults in contact with deaf children. This research should include studies of the nature of receptive and productive aspects of English-like signing in addition to aspects of auditory, oral language models.

- Identify deaf children who have language disorders by examining and describing the differences between normal and language-impaired deaf children.

- Study approaches and techniques for the training of hearing parents of deaf children to sign or to facilitate the development of their children's spoken language, including the use of Cued Speech.

- Identify and describe the processes of reorganization of the input language, particularly pidginization and creolization processes in language contact situations.

- Identify and describe the invention of gestural language systems without formal sign input and the relation of this process to eventual signed or spoken language development.

- Study approaches and techniques for evaluating the potential of new technology and intervention strategies (such as auditory prostheses, laser disk technology, computer-based training systems) for promoting spoken language acquisition by deaf children.

- Identify critical periods for both the natural acquisition and training of spoken or signed language by deaf children.

- Develop the means of identifying language disorders in deaf children from different cultures.

Studies of Literacy in Deaf Children and Adults

Because problems associated with the acquisition of reading and writing skills are the most pervasive academic and vocational consequences of deafness, studies of the acquisition of English literacy must be included as a primary research objective. Research should be conducted to:

- Study the nature of processing text by successful deaf readers in an attempt to identify the most effective strategies, both auditory and visual, for the teaching of literacy to deaf people.
- Develop and test new strategies and techniques for teaching English as a second language to deaf children who make use of their capabilities for visual language processing.
- Study the role of captioning, telecommunication devices, personal computers and other technological influences on the improvement of deaf children's literacy skills.
- Study the relationships between speech processing and literacy in deaf children who use spoken language primarily.
- Study the relationships among speech processing, sign processing and literacy in deaf children who use sign language.
- Develop and evaluate appropriate and psychometrically-sound tests of psychosocial, intellectual and academic development and of first- and second-language acquisition by deaf children and adults under a variety of language use conditions.
- Examine the interaction of acquisition of signed languages with spoken and written language and begin to characterize the the resulting bilingualism. Studies of the order of acquisition of speech and signed language as they affect children's eventual acquisition of English language and literacy should also be conducted.

Basic Research on Sign Language Structure and Function

Studies of the organization of the brain and its relation to language function, especially signed language, are needed. Research on how signed language acquisition interfaces with other biological and physical systems is also important. Investigators should be encouraged to:

- Continue research on brain mapping for sign language functions.
- Develop improved techniques for imaging sign language motions in three-dimensional space.
- Conduct further investigations into how deaf people perceive and process visually. Studies could include investigations of the relation between limb control and vision and of the functioning of deaf people with visual disorders.

- Conduct studies of the nature of parallel processing of language, such as the simultaneous processing of visual and auditory information.
- Expand studies of the brain and language, such as those on the specialization of the cerebral hemispheres for language and other cognitive processing.

Investigations of signed language structures are also important. Specifically, there should be attempts to:

- Study signed language and other languages used by the deaf community from functional/psychological and structural/linguistic perspectives. Studies should focus on the nature of the "creolization" of signed language and the effect of interaction of modality and language structure, including contact signing.
- Study signed languages other than ASL and varieties of signing within ASL, to identify the role of cultural and ethnic differences on signed language use by deaf people.
- Study other signed languages, such as simultaneous communication and signed English, relative to the acquisition of English language by deaf children.

The acquisition of the ability to employ a signed language depends on the development of a number of interrelated cognitive and linguistic abilities that contribute to the perception of sign. Interdisciplinary studies should be carried out to:

- Relate infants' early acquisition of sign language phonology, assessed through tests of sign perception, to the acquisition of the higher levels of language, such as the acquisition of words (lexicon), word meanings (semantics) and grammar (syntax).
- Investigate basic and higher level processes underlying vision, including the requirements of structured use of space and movement, the processing of complex dynamic arrays and the perception of motion and form.
- Study the impairments to sign perception in deaf individuals who become aphasic or who sustain other cognitive impairments subsequent to brain damage.

Language and Its Disorders in Children

A number of questions pertaining to normal language development in hearing children are not yet resolved. Although the sequence of language attainments is generally known, at least for English, the bases of some of the acquisition patterns are not yet fully understood. For example it is not yet clear the degree to which young children's early sentences involve abstract grammatical categories as opposed to semantically based notions. The degree to which language learning mechanisms are modular rather than dependent upon more general cognitive operations must also be determined. Issues requiring further investigation can be found for each developmental period.

The research needs for language disorders in children fall into four broad areas encompassing study of the bases of language disorders in children, investigations of assessment, studies of academic, social and vocational impact and investigations of intervention.

Bases of Language Disorders in Children

Many questions concerning the very nature of language disorders remain unanswered. Certainly, discovery of the bases of language impairment is necessary before meaningful steps toward prevention can be taken. Similarly, identification of these bases and their accompanying symptoms is required for the development of an accurate typology for language disorders in children. Accordingly, it is essential to investigate a range of factors that may be implicated, including characteristics of the language being acquired and factors that influence the production of speech. The language characteristics themselves should be examined with an eye toward how they contribute to our understanding of the child's difficulty. Research should be carried out to:

- Examine the linguistic profiles of language-impaired children to determine if they vary according to the type of language being acquired (e.g., morphologically rich vs. sparse; flexible vs. rigid word order). The weaknesses observed in language-impaired children across these languages might reveal a common factor that may be the source of the disorder.

- Examine the impact on language production of structural anomalies of the speech mechanism, such as craniofacial anomalies, long-standing tracheotomies or severe neuromotor impairment. The relative contribution of subtle motor speech problems to certain subtypes of language impairment is not known.

The neurogenic basis of developmental language disability is unknown in the vast majority of those with specific language impairment, as well as in those in whom these disorders are associated with other disabilities such as autism and mental retardation. The mechanisms by which neurogenic dysfunction occurs and the many genetic and acquired causes of developmental language dysfunction are still unresolved. A wide variety of intrinsic and/or extrinsic factors may be responsible for an initial induction of a

neurogenic abnormality. Research should be conducted to:

- **Study the normally developing brain across the lifespan using a wide range of anatomic, physiologic and metabolic techniques. New advances in imaging the brain (anatomic, physiologic and metabolic) are particularly important to apply to studies investigating normal and abnormal development.**

- **Conduct multidisciplinary studies that combine imaging techniques with fine-grained behavioral analysis of processes underlying language development and disorders.**

Advances in molecular genetics, coupled with recent evidence of familial transmission in some cases of developmental language and learning disability, suggest that further genetic studies would be particularly profitable. Studies should combine state-of-the-art behavioral assessment with molecular procedures to:

- **Determine the reason for the much higher prevalence of developmental language disorders in boys than girls.**

The precise role of nonlinguistic cognitive factors must also be examined in children with language disorders. Although many language-impaired children exhibit limitations in intelligence as it is broadly defined, it is likely that particular aspects of cognition are more important to language learning than others. For example, many studies of SLI children have found deficiencies in both symbolic and nonsymbolic domains of knowledge even when scores on standard intelligence tests are within the normal range. Further work is needed to:

- **Isolate those cognitive areas not represented in IQ tests and determine whether or not these areas interact with language functioning.**

- **Determine to what extent language impairment may be secondary to psychosocial disorders.**

- **Determine to what extent psychosocial disorders may result from a primary language impairment. There are special groups of children and youths who are at risk for language disorders and language-based learning disorders. These special groups include victims of abuse, neglect or drug- or alcohol-related lifestyles and homelessness and general victims of poverty.**

- **Determine to what extent failures in communication and education are related to psychosocial factors.**

Assessment

The purposes of assessment include the identification of a language

impairment as well as the determination of the nature and severity of the impairment, the prognosis and the initial goals for intervention. Initiatives are needed to:

- Develop psychometrically sound and culturally fair and sensitive procedures for the measurement of language comprehension and production to be used in identifying and classifying language impairments.
- Develop alternative assessment strategies including criterion-referenced testing, observational techniques, interview procedures and other informal strategies.
- Explore the utility of state-of-the-art computer technology in language assessment, including language sampling analysis.
- Develop assessment strategies which have application, validity and reliability for identifying language disorders in children in a variety of assessment contexts (e.g., school, home, clinic).
- Determine the most appropriate strategies for evaluating limited-English-proficient (LEP) children including the use of interpreters or informants.
- Develop assessment tools for preschool populations, especially for children under three years of age.

Academic, Social and Vocational Impact

The negative academic, social and vocational consequences of language disorders in children have been well documented; however, research is needed to:

- Study the relationship between language disorders and subsequent or concomitant learning disabilities.
- Study the relationship in children between language disorders and social adjustment problems.

Intervention

New intervention strategies for language-impaired children need to be developed that are capable of testing and refining current theoretical models. These approaches should also be tailored to meet the needs of individual children; that is, they should address documented, underlying perceptual and motor deficits as well as linguistic inadequacies. Furthermore, the strategies should be culturally relevant and salient to the individual child's experiences and future aspirations. Research must be conducted to:

- Develop new intervention strategies based upon current theoretical models and establish their efficacy.

- Determine the efficacy of currently available intervention strategies through both single subject studies and studies of children who clearly represent different types of language impairment.

- Evaluate alternative models of service delivery such as family or school-based programs versus direct delivery by speech-language pathologists.

- Investigate the use of computers and recent technologic advances (for example, in speech recognition and speech production) in intervention with language-impaired children and with deaf children learning oral language.

Language and Its Disorders in Adults

The research needs for adult language disorders fall into four broad areas encompassing research on language and the brain; cognitive and linguistic studies of the underlying functional sources of language disorders; investigations targeted at assessment and treatment of language disorders; and comparative study of language and its disorders in different populations.

Brain-Language Relations

Clearer understanding of the complex relationship between language processing and brain structure and function is essential to addressing a variety of crucial issues relating to language and its disorders in adults. Primary among these is a set of questions relating to recovery of language function. Individuals vary widely in their recovery of language capacities after apparently similar brain lesions and little is known about the mechanisms underlying this variability. Detailed study is needed to:

- Investigate the mechanisms by which recovery takes place and the basis for individual differences in recovery, using a variety of techniques for indexing brain activity in vivo (e.g., positron emission tomography, single photon emission computed tomography, event-related potentials).

- Clarify the role of the non-dominant (typically right) cerebral hemisphere in the assumption of language functions following damage to the dominant hemisphere.

- Relate specific symptoms to discrete brain regions using lesion analysis. A correlation between the breakdown of motor speech planning and structural brain lesions has been demonstrated, but other potentially localizable language skills (such as speech sound discrimination and oral word comprehension) are still inadequately mapped.

- Define by clinico-anatomic study the link between processes that are closely related to well-localized structures and those that are broadly distributed in the language zone.
- Identify well-defined forms of selective impairments through detailed study of individual cases, including careful analysis of brain lesions and of functional language impairment.
- Explore the role of various neurotransmitter systems in the mediation of particular language operations. The potential for pharmacological treatment follows directly from such understanding.

Analysis of Processes Underlying Language Disorders

The language impairments that result from brain damage reflect the dysfunction of one or more of the mechanisms that subserve normal language, whether spoken, written, or signed, including perceptual, motor, cognitive and specifically linguistic mechanisms. For example, the normal ability to read involves visual perceptual mechanisms, mechanisms that control attention to the relevant material on the page, memory components that store knowledge of words and linguistic mechanisms that compute the meanings of sentences. Damage to any one of these mechanisms will result in a reading impairment, the specific form of impairment being determined by the particular mechanism that is damaged. Thus, an understanding of the nature of the various forms of language disorders consequent to brain damage crucially depends on knowledge of normal-language and related processes and their disruption. Continued study is needed to:

- Extend recent progress in the cognitive sciences to an understanding of the structure of normal language processing. For example, techniques involving real-time analysis of normal-language processes should be adapted to examine the nature of language pathology.
- Distinguish the various forms of dysfunction that characterize oral/aural, written and signed languages through comparative study of impairments in those modalities.
- Elucidate the relationship between deficits that are specific to the language system and those that arise from perceptual, motor or other cognitive disorders and clarify their relative contributions to complex language impairments.

Information about such relationships could provide an important basis for the design of new treatments.

- Continue comparative analyses of disorders in different languages, on the assumption that language-specific differences in symptoms can help reveal the linguistic and cognitive mechanisms that subserve language processing.
- Develop artificial intelligence computer models that simulate normal language and its disorders.

Assessment, Intervention and Recovery

Approaches to the remediation of language disorders require objective and reliable information about the nature and stability of patients' symptoms. Assessment instruments that provide such information must be developed in light of new research findings that have clarified symptom and deficit relationships. Furthermore, intervention strategies to address patients' impairments should build upon emerging indications that some symptoms indicate specific functional deficits and should exploit new technologic innovations. Specific opportunities in these areas include efforts to:

- Demonstrate the efficacy and efficiency of the existing intervention strategies for aphasia treatment. Such demonstrations will require development of new approaches to the evaluation of efficacy which use both single subject and group methods.
- Revise and improve existing assessment procedures in order to bring them into line with current understanding of the relationship of patients' symptoms to causal underlying language deficits.
- Develop a workable diagnostic scheme that provides a rational basis for the classification of patients and for comprehensive characterization of their deficits.
- Develop functional assessment tools to evaluate the communicative abilities of language-impaired individuals.
- Study the patterns of symptoms in patients with disorders in which deterioration instead of improvement is the natural course, for example, in Alzheimer's disease. Identification of predictors of the course of progression of language disorders in such patients would contribute to their management and provide a basis for approaching intervention.
- Develop and evaluate computer-assisted instruction as an intervention strategy for working with aphasic individuals. In particular, strategies that capitalize on recent information concerning

the functional basis of specific language symptoms or that provide aphasic individuals with workable compensatory mechanisms should be developed.

- Develop and evaluate alternative and augmentative communication systems for adults with language deficits. Adults severely impaired in understanding and producing language may be capable of effective communication by alternative means, including computer-based systems.

- Investigate social and cultural factors that have the potential to affect treatment outcome and evaluate the relative contribution of these factors to individual differences in response to treatment.

Comparative Language Studies

Language disorders in adults can take a variety of forms, because the many causes of such disorders affect the system differently and because there are pre-existing differences among the individuals who develop language problems. This diversity of language symptoms provides an important research opportunity, as comparative study of the different forms of language impairment can provide information about the nature of underlying language mechanisms. New initiatives are needed to:

- Obtain normative data from healthy individuals of various ages to determine whether or not there are changes throughout the lifespan in the use of spoken, written or signed language.

- Develop normative data on adults from a range of social strata and linguistic and cultural backgrounds to provide a basis for addressing the contributions of sociocultural factors, bilingualism and normal aging to language impairments.

- Compare analysis of left- and right-brain damaged hearing subjects to determine the extent to which the right hemisphere may be involved in language use. Study brain-damaged users of sign language in order to understand hemispheric specialization for complex linguistic properties conveyed through spatial mechanisms.

- Study the differences that exist between the language disorders of focally brain-damaged patients and those that accompany more generalized brain dysfunction. Comparisons among the forms that language breakdown can take secondary to these various causes have suggested important functional dissociations, but further study is required to clarify the nature of and underlying bases for these differences.

- Develop normative data on the language functioning of diverse populations to provide a substantive basis for approaching their language disorders. The population of the United States is increasingly multilingual; as this population ages and its risks of stroke and consequent aphasia increases, there will be an increasing number of bilingual individuals with language disorders.

APPENDIX A

Public Law 100-553

Public Law 100-553
100th Congress

An Act

To amend the Public Health Service Act to establish within the National Institutes of Health a National Institute on Deafness and Other Communication Disorders.

Oct. 28, 1988
[S 1727]

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

National Deafness and Other Communication Disorders Act of 1988.
42 USC 201 note.

SECTION 1. SHORT TITLE.

This Act shall be cited as the "National Deafness and Other Communication Disorders Act of 1988".

SEC. 2. ESTABLISHMENT AND TRANSFER OF FUNCTIONS.

Title IV of the Public Health Service Act (42 U.S.C. 281 et seq.) is amended—

(1) in section 401(b)(1)—

(A) by striking "and Communicative" in subparagraph (J); and

(B) by adding at the end the following new subparagraph:

"(M) The National Institute on Deafness and Other Communication Disorders.";

(2) in the heading for subpart 10 of part C, by striking "and Communicative";

(3) in section 457—

(A) by striking "and Communicative"; and

(B) by striking "disorder, stroke," and all that follows and inserting "and disorder and stroke."; and

(4) in Part C, by adding at the end the following new subpart:

"Subpart 13—National Institute on Deafness and Other Communication Disorders

Education.
Research and development.
Public information.

"PURPOSE OF THE INSTITUTE

42 USC 285m.

"SEC. 464. The general purpose of the National Institute on Deafness and Other Communication Disorders (hereafter referred to in this subpart as the 'Institute') is the conduct and support of research and training, the dissemination of health information, and other programs with respect to disorders of hearing and other communication processes, including diseases affecting hearing, balance, voice, speech, language, taste, and smell.

"NATIONAL DEAFNESS AND OTHER COMMUNICATION DISORDERS PROGRAM

42 USC 285m-1.

"SEC. 464A. (a) The Director of the Institute, with the advice of the Institute's advisory council, shall establish a National Deafness and Other Communication Disorders Program (hereafter in this section referred to as the 'Program'). The Director or the Institute shall, with respect to the Program, prepare and transmit to the Director of NIH a plan to initiate, expand, intensify and coordinate activities of the Institute respecting disorders of hearing (including tinnitus) and

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other communication processes, including diseases affecting hearing, balance, voice, speech, language, taste, and smell. The plan shall include such comments and recommendations as the Director of the Institute determines appropriate. The Director of the Institute shall periodically review and revise the plan and shall transmit any revisions of the plan to the Director of NIH.

"(b) Activities under the Program shall include—

"(1) investigation into the etiology, pathology, detection, treatment, and prevention of all forms of disorders of hearing and other communication processes, primarily through the support of basic research in such areas as anatomy, audiology, biochemistry, bioengineering, epidemiology, genetics, immunology, microbiology, molecular biology, the neurosciences, otolaryngology, psychology, pharmacology, physiology, speech and language pathology, and any other scientific disciplines that can contribute important knowledge to the understanding and elimination of disorders of hearing and other communication processes;

"(2) research into the evaluation of techniques (including surgical, medical, and behavioral approaches) and devices (including hearing aids, implanted auditory and nonauditory prosthetic devices and other communication aids) used in diagnosis, treatment, rehabilitation, and prevention of disorders of hearing and other communication processes;

"(3) research into prevention, and early detection and diagnosis, of hearing loss and speech and language disturbances (including stuttering) and research into preventing the effects of such disorders on learning and learning disabilities with extension of programs for appropriate referral and rehabilitation;

"(4) research into the detection, treatment, and prevention of disorders of hearing and other communication processes in the growing elderly population with extension of rehabilitative programs to ensure continued effective communication skills in such population;

"(5) research to expand knowledge of the effects of environmental agents that influence hearing or other communication processes; and

"(6) developing and facilitating intramural programs on clinical and fundamental aspects of disorders of hearing and all other communication processes.

"DATA SYSTEM AND INFORMATION CLEARINGHOUSE

42 USC 285m-2. "SEC. 464B. (a) The Director of the Institute shall establish a National Deafness and Other Communication Disorders Data System for the collection, storage, analysis, retrieval, and dissemination of data derived from patient populations with disorders of hearing or other communication processes, including where possible, data involving general populations for the purpose of identifying individuals at risk of developing such disorders.

"(b) The Director of the Institute shall establish a National Deafness and Other Communication Disorders Information Clearinghouse to facilitate and enhance, through the effective dissemination of information, knowledge and understanding of disorders of hearing and other communication processes by health professionals, patients, industry, and the public.

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"MULTIPURPOSE DEAFNESS AND OTHER COMMUNICATION DISORDERS CENTER

42 USC 285m-3.

"SEC. 464C. (a) The Director of the Institute shall, after consultation with the advisory council for the Institute, provide for the development, modernization, and operation (including care required for research) of new and existing centers for studies of disorders of hearing and other communication processes. For purposes of this section, the term 'modernization' means the alteration, remodeling, improvement, expansion, and repair of existing buildings and the provision of equipment for such buildings to the extent necessary to make them suitable for use as centers described in the preceding sentence.

"(b) Each center assisted under this section shall—

"(1) use the facilities of a single institution or a consortium of cooperating institutions; and

"(2) meet such qualifications as may be prescribed by the Secretary.

"(c) Each center assisted under this section shall, at least, conduct—

"(1) basic and clinical research into the cause diagnosis, early detection, prevention, control and treatment of disorders of hearing and other communication processes and complications resulting from such disorders, including research into rehabilitative aids, implantable biomaterials, auditory speech processors, speech production devices, and other otolaryngologic procedures;

Health care professionals.

"(2) training programs for physicians, scientists, and other health and allied health professionals;

"(3) information and continuing education programs for physicians and other health and allied health professionals who will provide care for patients with disorders of hearing or other communication processes; and

"(4) programs for the dissemination to the general public of information—

"(A) on the importance of early detection of disorders of hearing and other communication processes, of seeking prompt treatment, rehabilitation, and of following an appropriate regimen; and

"(B) on the importance of avoiding exposure to noise and other environmental toxic agents that may affect disorders of hearing or other communication processes.

"(d) A center may use funds provided under subsection (a) to provide stipends for health professionals enrolled in training programs described in subsection (c)(2).

"(e) Each center assisted under this section may conduct programs—

"(1) to establish the effectiveness of new and improved methods of detection, referral, and diagnosis of individuals at risk of developing disorders of hearing or other communication processes; and

"(2) to disseminate the results of research, screening, and other activities, and develop means of standardizing patient data and recordkeeping.

Aged persons. Children and youth.

"(f) The Director of the Institute shall, to the extent practicable, provide for an equitable geographical distribution of centers assisted under this section. The Director shall give appropriate consideration

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to the need for centers especially suited to meeting the needs of the elderly, and of children (particularly with respect to their education and training), affected by disorders of hearing or other communication processes.

"(g) Support of a center under this section may be for a period not to exceed seven years. Such period may be extended by the Director of the Institute for one or more additional periods of not more than five years if the operations of such center have been reviewed by an appropriate technical and scientific peer review group established by the Director, with the advice of the Institute's advisory council, if such group has recommended to the Director that such period should be extended.

"NATIONAL INSTITUTE ON DEAFNESS AND OTHER COMMUNICATION DISORDERS ADVISORY BOARD

42 USC 285m-4 "SEC. 464D. (a) The Secretary shall establish in the Institute the National Deafness and Other Communication Disorders Advisory Board (hereafter in this section referred to as the 'Advisory Board').

"(b) The Advisory Board shall be composed of eighteen appointed members and nonvoting ex officio members as follows:

"(1) The Secretary shall appoint—

"(A) twelve members from individuals who are scientists, physicians, and other health and rehabilitation professionals, who are not officers or employees of the United States, and who represent the specialties and disciplines relevant to deafness and other communication disorders, including not less than two persons with a communication disorder; and

"(B) six members from the general public who are knowledgeable with respect to such disorders, including not less than one person with a communication disorder and not less than one person who is a parent of an individual with such a disorder.

Of the appointed members, not less than five shall by virtue of training or experience be knowledgeable in diagnoses and rehabilitation of communication disorders, education of the hearing, speech, or language impaired, public health, public information, community program development, occupational hazards to communications senses, or the aging process.

"(2) The following shall be ex officio members of each Advisory Board:

"(A) The Assistant Secretary for Health, the Director of NIH, the Director of the National Institute on Deafness and Other Communication Disorders, the Director of the Centers for Disease Control, the Chief Medical Director of the Veterans' Administration, and the Assistant Secretary of Defense for Health Affairs (or the designees of such officers).

"(B) Such other officers and employees of the United States as the Secretary determines necessary for the Advisory Board to carry out its functions.

"(c) Members of an Advisory Board who are officers or employees of the Federal Government shall serve as members of the Advisory Board without compensation in addition to that received in their regular public employment. Other members of the Board shall receive compensation at rates not to exceed the daily equivalent of the annual rate in effect for grade GS-18 of the General Schedule for each day (including traveltime) they are engaged in the performance of their duties as members of the Board.

"(d) The term of office of an appointed member of the Advisory Board is four years, except that no term of office may extend beyond the expiration of the Advisory Board. Any member appointed to fill a vacancy for an unexpired term shall be appointed for the remainder of such term. A member may serve after the expiration of the member's term until a successor has taken office. If a vacancy occurs in the Advisory Board, the Secretary shall make an appointment to fill the vacancy not later than 90 days from the date the vacancy occurred.

"(e) The members of the Advisory Board shall select a chairman from among the appointed members.

"(f) The Secretary shall, after consultation with and consideration of the recommendations of the Advisory Board, provide the Advisory Board with an executive director and one other professional staff member. In addition, the Secretary shall, after consultation with and consideration of the recommendations of the Advisory Board, provide the Advisory Board with such additional professional staff members, such clerical staff members, such services of consultants, such information, and (through contracts or other arrangements) such administrative support services and facilities, as the Secretary determines are necessary for the Advisory Board to carry out its functions.

"(g) The Advisory Board shall meet at the call of the chairman or upon request of the Director of the Institute, but not less often than four times a year.

"(h) The Advisory Board shall—

"(1) review and evaluate the implementation of the plan prepared under section 464A(a) and periodically update the plan to ensure its continuing relevance;

"(2) for the purpose of assuring the most effective use and organization of resources respecting deafness and other communication disorders, advise and make recommendations to the Congress, the Secretary, the Director of NIH, the Director of the Institute, and the heads of other appropriate Federal agencies for the implementation and revision of such plan; and

"(3) maintain liaison with other advisory bodies related to Federal agencies involved in the implementation of such plan and with key non-Federal entities involved in activities affecting the control of such disorders.

"(i) In carrying out its functions, the Advisory Board may establish subcommittees, convene workshops and conferences, and collect data. Such subcommittees may be composed of Advisory Board members and nonmember consultants with expertise in the particular area addressed by such subcommittees. The subcommittees may hold such meetings as are necessary to enable them to carry out their activities.

Reports.

"(j) The Advisory Board shall prepare an annual report for the Secretary which—

"(1) describes the Advisory Board's activities in the fiscal year for which the report is made;

"(2) describes and evaluates the progress made in such fiscal year in research, treatment, education, and training with respect to the deafness and other communication disorders;

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"(3) summarizes and analyzes expenditures made by the Federal Government for activities respecting such disorders in such fiscal year; and

"(4) contains the Advisory Board's recommendations (if any) for changes in the plan prepared under section 464A(a).

"(k) The National Deafness and Other Communication Disorders Advisory Board shall be established not later than 90 days after the date of the enactment of the National Institute on Deafness and Other Communication Disorders Act.

"INTERAGENCY COORDINATING COMMITTEE

42 USC 285m-5. "SEC. 464E. (a) The Secretary may establish a committee to be known as the Deafness and Other Communication Disorders Interagency Coordinating Committee (hereafter in this section referred to as the 'Coordinating Committee').

"(b) The Coordinating Committee shall, with respect to deafness and other communication disorders—

"(1) provide for the coordination of the activities of the national research institutes; and

"(2) coordinate the aspects of all Federal health programs and activities relating to deafness and other communication disorders in order to assure the adequacy and technical soundness of such programs and activities and in order to provide for the full communication and exchange of information necessary to maintain adequate coordination of such programs and activities.

"(c) The Coordinating Committee shall be composed of the directors of each of the national research institutes and divisions involved in research with respect to deafness and other communication disorders and representatives of all other Federal departments and agencies whose programs involve health functions or responsibilities relevant to deafness and other communication disorders.

"(d) The Committee shall be chaired by the Director of NIH (or the designee of the Director). The Committee shall meet at the call of the chair, but not less often than four times a year.

Reports. "(e) Not later than 120 days after the end of each fiscal year, the Committee shall prepare and transmit to the Secretary, the Director of NIH, the Director of the Institute, and the advisory council for the Institute a report detailing the activities of the Committee in such fiscal year in carrying out subsection (b).

"LIMITATION ON ADMINISTRATIVE EXPENSES

42 USC 285m-6. "SEC. 464F. With respect to amounts appropriated for a fiscal year for the National Institutes of Health, the limitation established in section 408(b)(1) on the expenditure of such amounts for administrative expenses shall apply to administrative expenses of the National Institute on Deafness and Other Communication Disorders.".

42 USC 285m note. Gifts and property. Contracts. Records. **SEC. 3. TRANSITIONAL AND SAVINGS PROVISIONS.**

(a) TRANSFER OF PERSONNEL, ASSETS, AND LIABILITIES.—Personnel employed by the National Institutes of Health in connection with the functions vested under section 2 in the Director of the National Institute on Deafness and Other Communication Disorders, and assets, property, contracts, liabilities, records, unexpended balances of appropriations, authorizations, allocations, and other funds of the National Institutes of Health, arising from or employed, held, used,

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available to, or to be made available, in connection with such functions shall be transferred to the Director for appropriate allocation. Unexpended funds transferred under this subsection shall be used only for the purposes for which the funds were originally authorized and appropriated.

Grants.
Contracts.

(b) SAVINGS PROVISIONS.—With respect to functions vested under section 1 in the Director of the National Institute on Deafness and Other Communication Disorders, all orders, rules, regulations, grants, contracts, certificates, licenses, privileges, and other determinations, actions, or official documents, that have been issued, made, granted, or allowed to become effective, and that are effective on the date of the enactment of this Act, shall continue in effect according to their terms unless changed pursuant to law.

Approved October 28, 1988.

LEGISLATIVE HISTORY—S. 1727 (H.R. 3361):

HOUSE REPORTS: No. 100-761 accompanying H.R. 3361 (Comm. on Energy and Commerce).

CONGRESSIONAL RECORD, Vol. 134 (1988):
Oct. 7, considered and passed Senate.
Oct. 13, considered and passed House.

APPENDIX B

National Strategic Research Plan

Expert Panel Members

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